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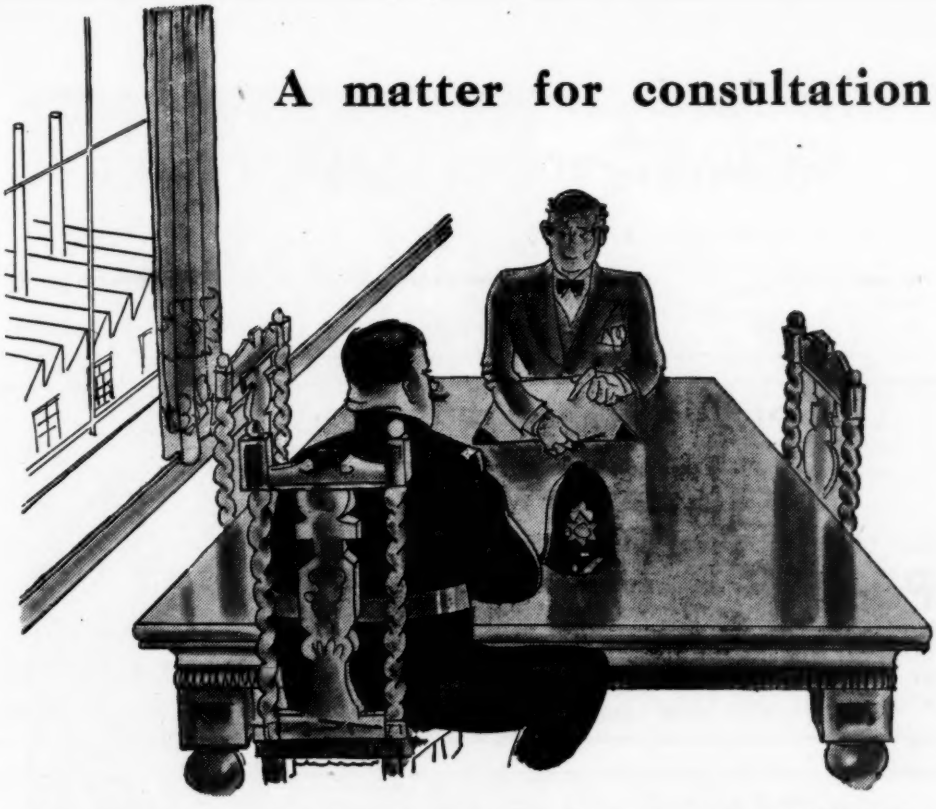

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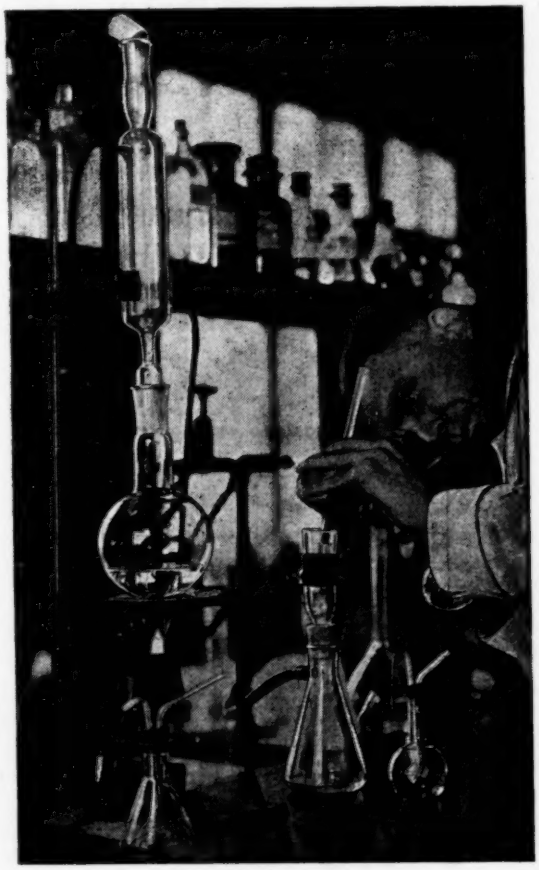

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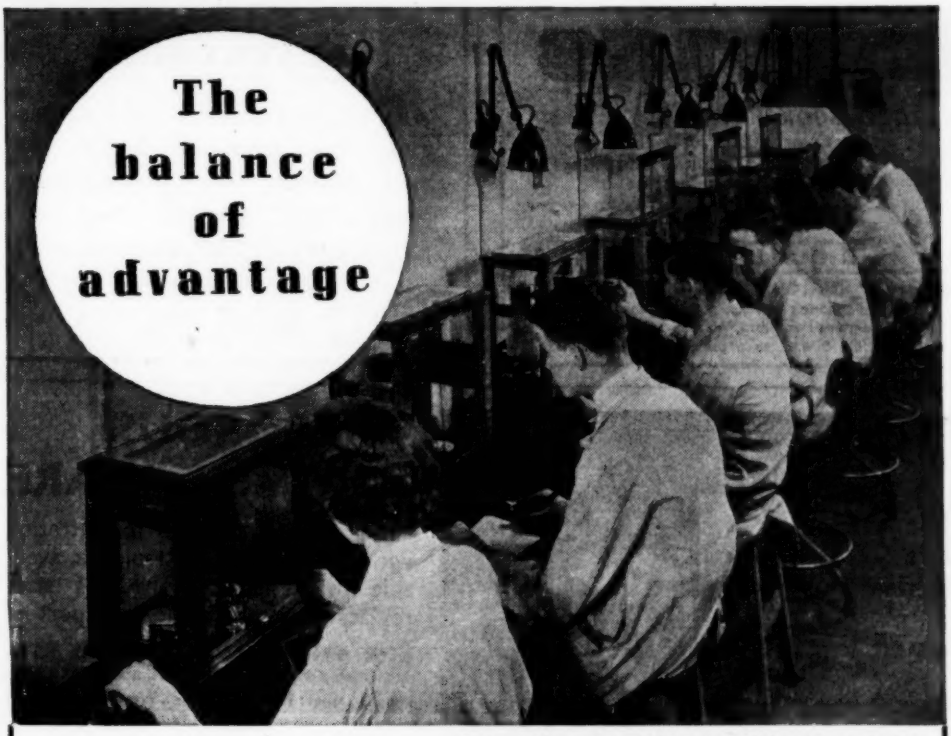

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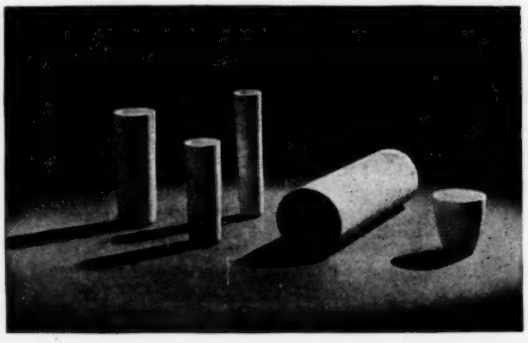

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meeting with the University College Physical and Chemical Society). These meetings were held at University College.

St. Andrews and Dundee. 26th April, at University College, *Lecture*, "The Structure and Chemistry of Metallic Crystals," by Professor G. D. Preston.

Sheffield. 9th February, *Lecture*, "Non-Benzenoid Aromatic Systems," by Professor W. Baker (joint meeting with the University Chemical Society); 11th May (joint meeting with the University Chemical Society and the South Yorkshire Section of the R.I.C.), *Lecture*, "Recent Developments in Petroleum Technology," by Dr. A. E. Dunstan; 25th May, *Lecture*, "The Place of the Resonance Concept in Chemistry," by Mr. R. P. Bell; 26th October (joint meeting with the South Yorkshire Section of the R.I.C.), *Lecture*, "Burner Flames," (a) "Quiescent Flames," by Professor D. T. A. Townend, (b) "Turbulent Flames," by Dr. J. E. Garside; 16th November (joint meeting with the University Chemical Society), *Lecture*, "Our War Against Insect Pests," by Professor I. M. Heilbron. These meetings were held at the University.

South Wales. 18th January, at University College, Swansea, *Lecture*, "Some Consequences of Hydrogen Bond Formation," by Professor W. Baker; 24th May, at University College, Cardiff, *Hugo Müller Lecture*, "The Past and Future of Crystal Chemistry," by Professor J. D. Bernal; 7th November, at Newport Technical College (joint meeting with the local sections of the R.I.C. and the S.C.I.), *Lecture*, "Research on Coal Tar," by Mr. E. A. Coulson and Mr. J. I. Jones; 23rd November, at University College, Cardiff (joint meeting with the local sections of the R.I.C. and the S.C.I.), *Lecture*, "Colchicine: its Chemistry and Biological Effects," by Professor J. W. Cook.

82. *The Crystal Structure of Tribromo(trimethylphosphine)gold.*

By M. F. Perutz and (Miss) O. Weisz.

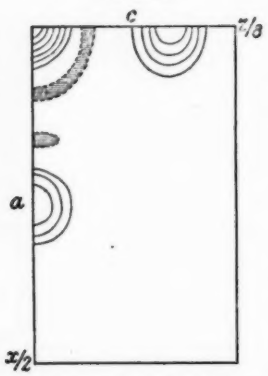
The crystal structure of PMe_3–$AuBr_3$ was determined by the usual methods of *X*-ray analysis. The crystals are orthorhombic, with eight molecules in the unit cell, and belong to the space-group *Pbca*. Trial-and-error as well as Fourier methods were employed in order to determine the positions of the molecules. The parameters finally assigned to the gold and bromine atoms were checked by comparison between observed and calculated structure amplitudes of the *h*0*l*, 0*kl* and 3*kl* reflections which were found to be in good agreement. The position of the phosphine groups had to be inferred from considerations of optimum packing. The crystal structure is of the layer type, with molecules in neighbouring layers pointing in opposite directions. The co-ordination around the auric gold atoms is planar, in conformity with the findings of previous investigators, and the gold–bromine distance is 2·5 A.

This structure analysis was begun at the suggestion of Dr. F. G. Mann, who had observed that certain derivatives of four-covalent auric gold failed to show the geometric isomerism which their (probable) planar structure and their method of preparation would lead one to expect (Mann and Purdie, *J.*, 1940, 1235). Compounds of 2-covalent aurous gold were known to have a linear structure (*e.g.*, $AsEt_3$–AuCl; Mann, Wells, and Purdie, *J.*, 1937, 1835), whereas derivatives of 4-covalent auric gold have a planar structure (Buraway, Gibson, Hampson, and Powell, *J.*, 1937, 1690; Phillips and Powell, *Proc. Roy. Soc.*, 1939, *A*, **173**, 147; see also Elliot and Pauling, *J. Amer. Chem. Soc.*, 1938, **60**, 1946). The compound PEt_3–$AuBrI_2$ should therefore exist in the form of two geometric isomers, (I) and (II), depending on whether it is prepared by the addition of iodine to PEt_3–AuBr or of iodine monobromide to PEt_3–AuI. When Mann and Purdie failed to obtain the expected

cis- and *trans*-forms, either of this compound or of three other related ones, they were forced to conclude either that the co-ordination around the gold atom is tetrahedral, or more probably, that the groups around the gold atom have a certain mobility and tend to take up the most stable configuration, no matter how the compound is prepared.

The calculation of a single Fourier projection of PMe_3–$AuBr_3$ sufficed to show that the co-ordination around the gold atom is, in fact, planar, and that Mann and Purdie's second suggestion must therefore account for the absence of stereoisomerism in trihalide compounds containing different halogen atoms. Although the point at issue was thus settled without any need to resort to a complete structure analysis, it was nevertheless decided to carry our investigation one stage further and to establish the main interatomic distances and general manner of packing of the molecules in the crystal. Fourier syntheses as well as trial-and-error methods were used to work out the parameters of gold and bromine; the positions of the carbon and phosphorus atoms, on the other hand, had to be inferred from considerations of packing, because their relative scattering contribution was too feeble to have a measurable influence on the intensities of any of the observed reflections.

Fig. 1.



Relative electron-density projection on (010), *showing one-sixteenth of the unit cell. Contours of equal electron density are drawn at arbitrary intervals, every alternate contour on the gold atom being omitted; the lowest contour is shown as a dashed line. The shaded areas indicate electron-density troughs due to the diffraction effects of the two superimposed gold atoms.*

Details of Analysis.—Dr. Mann kindly supplied the crystals, which are lath-shaped, orthorhombic, yellow needles showing straight extinction on all faces and marked dichroism in two planes. The vibration direction of greatest light absorption is parallel to [100] and coincides with the vibration direction of the slowest ray, indicating that the molecules in the crystal lattice are arranged with their length along the *a* axis. This was subsequently confirmed by *X*-ray analysis. The unit cell-dimensions were determined by oscillation photographs taken about the three axes; they are $a = 9{\cdot}0_6$, $b = 9{\cdot}8_5$, $c = 22{\cdot}0_5$ A. The density of the crystals as determined by pyknometer methods is 3·37 g./c.c., giving eight molecules per unit cell. A pseudo-cell containing only two molecules is indicated, however, by the extreme weakness of the odd layer lines on photographs taken with *b* and *c* as rotation axes.

The oscillation photographs showed that there are no absences of the general type *hkl*. The special absences 0*kl* for *k* odd, *h*0*l* for *l* odd, and *hk*0 for *h* odd were found and later confirmed on Weissenberg photographs taken about the three axes; these gave the space-group unambiguously as *Pbca*. In addition to the space group absences, *h*0*l* reflections were found to be missing for $h + \frac{l}{2} = 2n + 1$, a feature of the *X*-ray pattern which greatly simplified the analysis and actually provided the clue to the disposition of the molecules on the *b* projection.

There was, in fact, only one set of molecular positions which would account for the absence of those reflec-

tions: the molecules had to be placed with their length along the *a* axis, in the positions $z = 1/8$, $z = 3/8$, etc. It can be seen in Fig. 2 that this brings the molecules to the corners and the centre of the "halved" *b* face—the two halves from $z = 0$ to $z = \frac{1}{2}$ and from $z = \frac{1}{2}$ to $z = 1$ appearing identical in projection. Moreover, a one-dimensional Patterson projection on [100] indicated that the gold atoms lie at $x = \frac{1}{4}$ and $x = \frac{3}{4}$, thus leaving only four positions for the eight gold atoms in the unit cell; the gold atoms of pairs of molecules related by the *b* glide planes therefore come to be superimposed, with the result that the relative scattering contribution of these "doubled" gold atoms outweighs the combined contributions of all the other atoms in the unit cell and thus determines the phases of all *h*0*l* reflections. A Fourier projection on the *x*, *z* plane could therefore be calculated without having to make any further assumptions about the structure (Fig. 1).

Visually estimated relative intensities obtained from Weissenberg photographs were used to determine the values of F'_{h0l}; the result of the Fourier summation shows, of course, the gold and bromine atoms but not the phosphine groups. A foreshortening of one of the gold–bromine distances indicates that the plane of the molecule is inclined to the plane of the projection. The *x* and *z* co-ordinates of the gold and bromine atoms derived from this Fourier projection were confirmed by comparison of calculated and observed F's, which agreed satisfactorily (Table I*a*). In these calculations it was assumed that the phosphorus peak is

TABLE I.

Comparison of observed and calculated structure amplitudes, arranged in order of decreasing values of θ.

$$F' \text{ calc.} = \frac{1}{10} Fe^{-2 \sin^2\theta/\lambda^2}, \quad F' \text{ obs.} = k \sqrt{I_R \frac{1 + \cos^2 2\theta}{\sin 2\theta}},$$

where I_R represents the visually estimated relative intensity of the reflection on the Weissenberg photograph and k is an arbitrary factor determined from the equation

$$k_{h0l} = \Sigma F' \text{ calc.} / \Sigma \sqrt{I_R \frac{1 + \cos^2 2\theta}{\sin 2\theta}}.$$

The quality of the agreement in each case is shown by the expression

$$\Sigma \Delta F'_{h0l} / \Sigma F'_{h0l}, \text{ calc.}$$

where $\Delta F'$ is the numerical difference between F' calc. and F' obs. No corrections for absorption or extinction were applied.

TABLE I*a*.

$k_{h0l} = 13{\cdot}5$; $\Sigma \Delta F'_{h0l} / \Sigma F'_{h0l}$, calc. = 0·20.

Absences of the type $F'_{h0l} = 0$ for $h + \frac{l}{2} = 2n + 1$ are omitted.

Index.	F', calc.	F', obs.	Index.	F', calc.	F', obs.	Index.	F', calc.	F', obs.	Index.	F', calc.	F', obs.
102	− 77	53	502	−38	40	2,0,16	+ 3	0	5,0,18	− 2	0
004	− 64	57	3,0,10	−70	66	702	−53	47	7,0,14	+33	27
200	+ 72	59	408	+46	54	706	+19	28	902	−16	19
204	− 2	0	2,0,12	−47	53	5,0,14	+20	28	1,0,22	+32	43
106	+ 3	0	506	+ 6	0	4,0,16	+22	30	4,0,20	−28	30
302	− 85	86	1,0,14	+38	51	6,0,12	−39	32	8,0,12	−36	26
008	+ 65	55	600	+51	43	3,0,18	−14	19	3,0,22	+36	36
306	+ 22	20	604	− 9	0	800	+47	42	0,0,24	+39	35
208	+ 10	0	4,0,12	−72	72	7,0,10	−47	36	2,0,24	+20	31
400	+104	108	3,0,14	+45	49	804	−17	27	6,0,20	−11	0
1,0,10	− 64	74	5,0,10	−21	38	0,0,20	−35	35	5,0,22	+21	23
404	+ 43	61	0,0,16	+29	35	2,0,20	−10	0	8,0,16	+ 9	18
0,0,12	− 92	104	608	+14	0	808	+20	30	4,0,24	+33	31
						6,0,16	+ 3	0			

TABLE I*b*.

$k_{0kl} = 33{\cdot}3$, except for $k_{0k0} = 14{\cdot}2$; $\Sigma \Delta F'_{0kl} / \Sigma F'_{0kl}$, calc. = 0·26.

Absences of the type $F'_{0kl} = 0$ for $l = 2(2n + 1)$ are omitted.

Index.	F', calc.	F', obs.	Index.	F', calc.	F', obs.	Index.	F', calc.	F', obs.	Index.	F', calc.	F', obs.
004	−64	53	061	+27	27	0,4,15	−19	0	0,4,20	−30	36
021	−11	13	0,2,13	+10	0	0,2,17	0	0	0,8,13	+18	10
023	+37	33	049	+ 6	0	0,6,12	+50	57	0,10,1	+ 7	0
024	+71	73	063	+14	0	081	− 4	0	0,10,3	+ 9	10
025	− 0	13	064	+31	53	083	−24	20	0,10,5	−18	20
008	+65	70	0,4,11	−11	10	0,4,16	+45	57	0,8,15	+ 5	0
027	+ 5	13	065	− 4	0	084	−32	53	0,10,7	−17	17
041	−20	17	0,4,12	−35	37	085	+16	0	0,10,9	+ 6	7
028	−78	80	067	− 5	0	0,6,13	−17	17	0,8,16	+22	27
043	+ 7	0	068	−34	53	087	+13	0	0,0,24	+39	40
044	−74	77	0,2,15	−20	20	088	+27	47	0,2,24	−21	20
029	+28	23	0,4,13	+18	0	0,0,20	−35	40			
045	+26	23	0,0,16	+29	50	0,6,15	− 6	0	020	−66	55
047	+29	20	069	+ 3	0	0,2,20	+35	47	040	+49	45
0,2,11	+ 2	0	0,2,16	−55	63	0,8,11	− 7	0	060	−72	77
0,0,12	−94	100	0,6,11	+22	17	0,6,16	−18	30	080	+23	38
0,2,12	+44	63				0,8,12	−18	33	0,10,0	−18	30

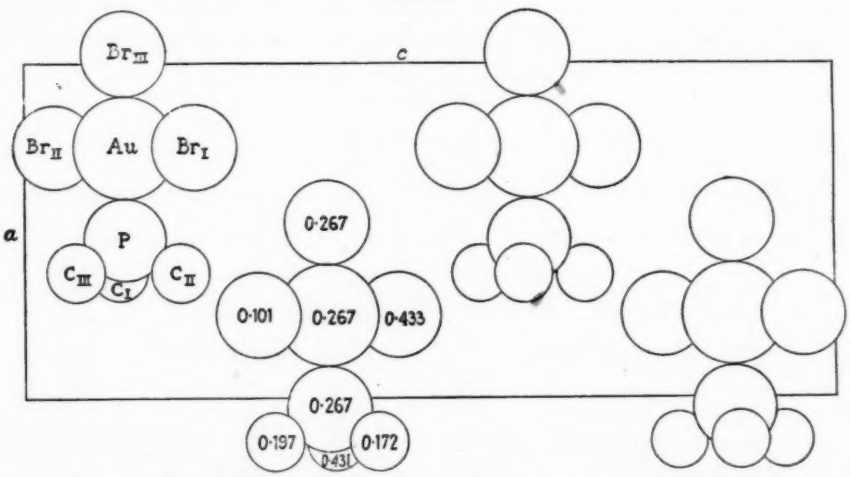
TABLE Ic.

$k_{2kl} = 11{\cdot}0$; $\Sigma\Delta F'_{2kl}/\Sigma F'_{2kl}$, calc. = 0·26.
Absences of the type $F'_{2kl} = 0$ for $l = 4n$ are omitted.

Index.	F′, calc.	F′, obs.	Index.	F′, calc.	F′, obs.	Index.	F′, calc.	F′, obs.	Index.	F′, calc.	F′, obs.
302	−84	137	326	−72	78	347	− 1	0	3,4,14	+29	24
311	+ 1	13	327	+10	18	349	+ 6	19	3,6,10	+38	29
312	+23	18	341	+ 5	0	3,4,10	−31	30	3,0,18	−14	0
313	− 2	0	319	+12	14	361	+19	15	381	− 8	0
321	+17	18	342	−40	37	362	+41	47	382	−18	28
322	+52	50	343	− 9	24	363	−11	18	383	+15	0
323	−27	25	3,0,10	−70	75	3,0,14	+45	53	3,2,18	+37	28
315	− 2	9	329	+22	22	365	− 1	0	386	+25	24
306	+22	27	3,1,10	+ 7	0	3,2,14	−35	31	3,6,14	−26	22
325	−16	16	345	+ 6	0	366	−12	22	3,4,18	−32	22
316	−12	13	346	+57	63	367	+ 1	0	3,8,10	−14	21
317	+ 2	0	3,2,10	+36	41						

superimposed on one of the bromine peaks, and that the gold–phosphorus distance is 2·5 A., the sum of the atomic radii. Fig. 2 is drawn on the basis of the Fourier projection, as far as the gold and bromine atoms are concerned, and shows the arrangement of the molecules.

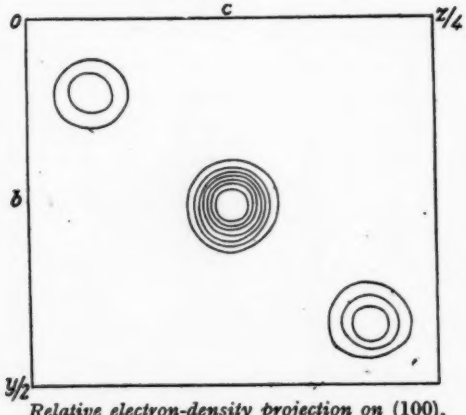
FIG. 2.



Unit cell projected on (010). *The meaning of the different circles is indicated on the molecule in the left-hand top corner. For the sake of clarity only one of the two layers of molecules in the unit cell is shown. The molecules in the second layer would show* Au, Br_I, *and* Br_{II} *in identical positions, while the positions of* Br_{III} *and the phosphine groups would be interchanged. The figures indicate* y *co-ordinates.* (1 *cm.* = 2 A.)

It now remained to find the *y* parameters of the gold and bromine atoms, and the *a* projection was chosen as the most suitable for this purpose. The relative intensities of the 0*kl* reflections, again read from Weissenberg photographs, were first used to calculate a Patterson projection from which the gold–bromine vector could at once be derived; its length was 2·5 A. and it enclosed an angle of 41° with the *c*-axis. Having thus determined the only intramolecular vector which appears on the *a* projection, we found the *y* parameter of the gold atom in the following way. It has been mentioned above that the weakness of reflections with odd *l* indices indicated the existence of a pseudo-cell with only half the length of *c*. In this pseudo-cell all the gold atoms would have to lie in two parallel planes which are normal to the *b* axis and separated by $\frac{1}{2}y$. In order to derive the real cell it was merely necessary to move the gold atoms from these ideal positions by a small displacement along the *y* axis, which was first determined approximately by trial-and-error methods. The parameters so obtained were then used to work out the signs of the F'_{0kl} coefficients, and a Fourier projection on the *a* plane was calculated (Fig. 3). The position of the gold peak on this projection indicates the magnitude of the shift from the layer plane to be

FIG. 3.

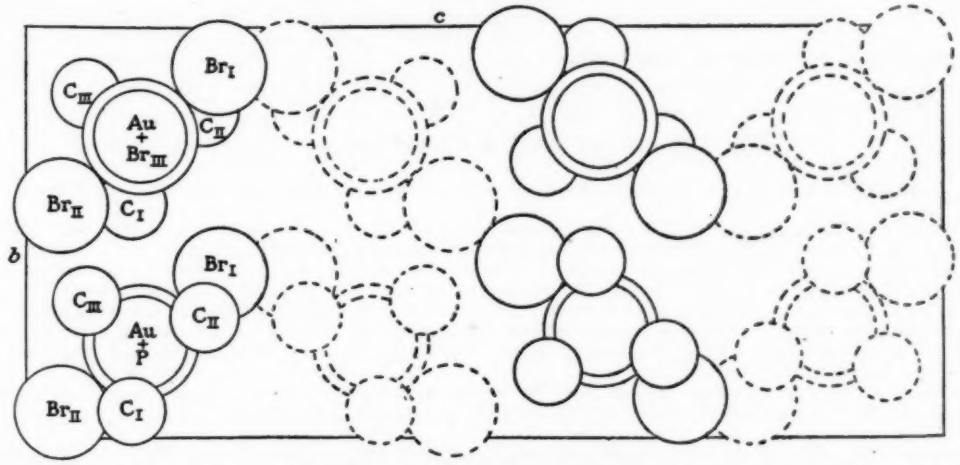


Relative electron-density projection on (100), *showing one quarter of the unit cell. Contours and scale as in Fig.* 1.

0·017*y*, and the angle between *z* and the plane of the molecules to be 41°, parameters which gave good agreement between observed and calculated structure amplitudes (Table I*b*). It was noticed that all the observed values of F'_{0k0} considerably exceed the calculated ones; this effect was attributed to reduced absorption in the case of the 0*k*0 reflections, due to the plate-like character of the crystals. If the intensities of all 0*k*0 reflections are scaled down by a common factor, agreement between observed and calculated structure amplitudes of these can be obtained. The general arrangement of the molecules in the *a* projection is illustrated in Fig. 4.

It should be noted that it is impossible, on the basis of either the *a* or the *b* projections, to distinguish between two arrangements of the molecules which appear identical when viewed in projection, but are very different from each other in space. In one case the molecules are placed at $y = \frac{1}{4} \pm 0{\cdot}017$ and $y = \frac{3}{4} \pm 0{\cdot}017$, while in the other case they come to lie at $y = \pm 0{\cdot}017$ and $y = \frac{1}{2} \pm 0{\cdot}017$; this implies a choice between the alternatives of either making the phosphine groups of all the molecules within any one layer point in the same direction, and of reversing their orientation on passing from one layer to the next, or of making every other pair of molecules within the *same* layer point in opposite directions. In order to decide between these two structures an equi-inclination Weissenberg photograph of the 3*kl* reciprocal lattice plane was taken. A comparison of the observed intensities with those calculated on the basis of the two alternative structures led to the conclusion that the first set of parameters mentioned above is the correct one, *i.e.*, that the phosphine groups of all the molecules lying within the same plane point in the same direction. Agreement between observed and calculated structure amplitudes was generally satisfactory, as shown in Table I*c*, and provided additional support for the correctness of the structure.

FIG. 4.



Unit cell projected on (100). *Full circles represent atoms at the height* x, *dashed circles represent atoms at* $x + \frac{1}{2}$. *The molecules are here seen end-on, with the* Br_{III}*'s in the top layer and the phosphine groups in the bottom layer pointing towards the observer.* (1 *cm.* = 2 A.)

TABLE II.

Atomic parameters and interatomic distances.

	Parameters. *x.*	*y.*	*z.*	Intramolecular distances, A.		Intermolecular distances, A.	
Au	0·250	0·267	0·125	Au–Br	$2{\cdot}5_0$	C_I–Br_{II}	$3{\cdot}6_1$
Br_I	0·250	0·101	0·212	Au–P	$2{\cdot}5_9$	C_I–Br_{III}	$3{\cdot}5_5$
Br_{II}	0·250	0·433	0·038	Br_{II}–C_I	$3{\cdot}8_4$	C_{III}–Br_{II}	$3{\cdot}4_3$
Br_{III}	0·026	0·267	0·125	Br_I–C_{III}	$3{\cdot}5_5$	C_{III}–Br_{III}	$3{\cdot}5_5$
P	0·526	0·267	0·125	Br_{III}–C_I	$3{\cdot}5_3$	C_{II}–Br_{II}	$3{\cdot}4_3$
C_I	0·625	0·431	0·119	Br_{II}–C_{II}	$4{\cdot}1_0$	C_{II}–Br_{II}	$3{\cdot}6_1$
C_{II}	0·625	0·197	0·193			C_{II}–C_I	$3{\cdot}4_3$
C_{III}	0·625	0·172	0·065				

To locate the positions of the methyl groups a model of the structure was built; it was assumed that the co-ordination around the phosphorus atom is tetrahedral, and the carbon–phosphorus distance is 1·87 A. The need for avoiding an unduly close approach between any pair of methyl groups and bromine atoms made it possible to define the orientation of the phosphine groups within comparatively narrow limits. The most probable carbon positions were finally calculated by rotating the phosphine groups until all C–Br distances were as nearly as possible equal; they are indicated in Table II, which shows the prominent interatomic

distances as well as the final co-ordinates of the atoms in the unit cell; the methyl groups are also shown in the drawings of the structure in Figs. 2 and 4.

Conclusions.—Crystals of PMe_3–$AuBr_3$ possess a layer structure. The layers lie normal to the *b* axis and are slightly less than 5 A. apart. The long axis of the molecules is parallel to the *a* axis, with the phosphine groups of all the molecules within any one layer pointing in the same direction; this orientation is reversed on passing from one layer to the next. The bromine atoms are arranged at three corners of a square which has the gold atom as its centre and is inclined at 41° to the plane of the layers. The gold–bromine distance, 2·5 A., is slightly smaller than that found by Burawoy, Gibson, Hampson, and Powell (*loc. cit.*) in their preliminary structure analysis of diethylmonobromogold. The structure is of the same general type as those of four-co-ordinated gold and palladium compounds described by previous investigators (see, *e.g.*, Mann and Wells, *J.*, 1938, 702; Wells, *Proc. Roy. Soc.*, 1938, A, **167**, 169) and provides further support for the square co-ordination of the four covalencies in compounds of auric gold.

We thank Dr. H. Lipson for his advice and helpful criticism and for the interest he took in this work. We are grateful to Dr. F. G. Mann for suggesting this problem to us and providing the crystals.

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83. *Reactions of Thermochromic Ethylenes.*

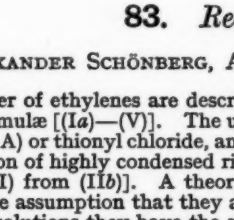
ALEXANDER SCHÖNBERG, ABDEL FATTAH ALY ISMAIL, and (in part) (MISS) W. ASKER.

A number of ethylenes are described which show physical and chemical properties in accordance with the classical formulæ [(I*a*)—(V)]. The unexpected properties discussed are thermochromism, cleavage with sulphur (see scheme A) or thionyl chloride, and photochemical reactions partly in sunlight. These photoreactions lead to the formation of highly condensed ring systems by the loss of hydrogen atoms from aromatic nuclei [*e.g.*, formation of (XI) from (II*b*)]. A theory is advanced to explain the strange behaviour of these ethylenes: it is based on the assumption that they are true ethylenes in the classical sense at low temperature, but in the melt and in hot solutions they have the structure of betaines [see, *e.g.*, (III) and (VIII) in the case of dixanthylen]; the theory of resonance is applied.

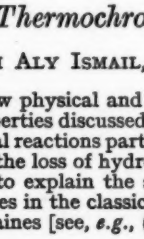
A similar explanation is advanced for the observation that some of the above-mentioned ethylenes, *viz.*, (I*b*), (II*a*), and (II*b*), change their colour when subjected to pressure (piezochromism).

THE substances (I*a*)—(V) show remarkable physical and chemical properties; in the crystalline state their colour is different from that of the melts and the solutions. Dixanthylen (III) is colourless at the temperature of liquid air and almost colourless at room temperature; the crystals turn bluish-green on heating, and both the melt and the hot solution are bluish-green (Schönberg and Schütz, *Ber.*, 1928, **61**, 478).

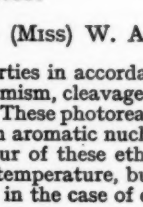
Diphenylmethyleneanthrone (I*a*) (Padova, *Compt. rend.*, 1906, **143**, 122), *di*-p-*anisylmethyleneanthrone* (I*b*), and diflavylen (IV) * form light yellow crystals at the temperature of liquid air, at room temperature they are yellow, the melts are ruby-red, and the colour of the hot solutions varies from orange-red to deep red depending on the concentrations.



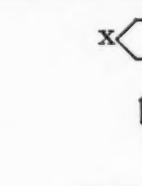
(I*a*, X = H; I*b*, X = OCH_3.)



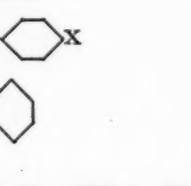
(II*a*, X = CO; II*b*, X = O.)



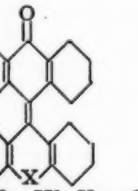
(III.)



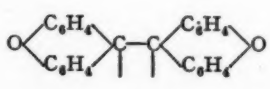
(IV.)



(V.)



(VI.)



(VII.)

The crystals of diphenylmethylenexanthen (V) are colourless at room temperature but orange-red when molten, and the hot solutions are orange (Schönberg and Nickel, *Ber.*, 1931, **64**, 2323).

Dianthraquinone (II*a*) is light yellow at the temperature of liquid air, citron-yellow at room temperature, green when molten, and bluish-green in hot solutions (Meyer, *Monatsh.*, 1909, **30**, 174), and 10-(9′-*xanthylen*)-*anthrone* (II*b*) is light yellow, yellowish-green, deep green, and deep bluish-green, respectively, under these four conditions.

Some of the above ethylenes form solutions the colour of which changes strongly with temperature; *e.g.*,

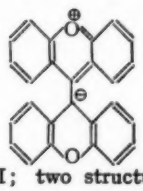
* Reactions denoted by an asterisk were carried out by Miss Asker.

solutions of (II*a*) and (II*b*) in benzonitrile, anisole, or xylene change from yellow or yellowish-green to bluish-green on heating. These colour changes are reversible.

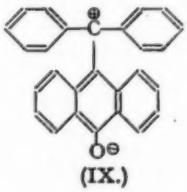
Under a pressure of *ca.* 100 kg./mm.², some of the above ethylenes also undergo a remarkable change of colour. This phenomenon was first observed by Meyer (*loc. cit.*), who found that the yellow crystals of (II*a*) become bluish-green on pressing. Similarly, (IV) changes from yellow to dark red (Schönberg and Asker, J., 1942, 272), (I*b*) from yellow to deep red, and (II*b*) from yellowish-green to deep green. For this phenomenon the name " piezochromism " is proposed. Very little is known about it, but Löwenbein observed (*Ber.*, 1927, **60**, 1855) that some solid ethanes seem to dissociate into free radicals when subjected to high pressures, for the solid assumes the colour of the radical. This would indicate that one molecule of the ethane occupies more space than two single radicals.

Theories of Thermochromism and Piezochromism.—It is well known that certain crystals (colourless or coloured), *e.g.*, nitrosobenzene, give melts or solutions of markedly different colour, the change being ascribed to depolymerisation; and Padova (*loc. cit.*), who found that (I*a*) (yellow) gives deep red solutions in neutral solvents, believed that the reversible colour change was due to polymerisation and depolymerisation, but this was disproved by Bergmann and Corte (*Ber.*, 1933, **66**, 39).

Ingold and Marshall (J., 1926, 3080), finding that the nearly colourless 9 : 10-diphenylanthracene gave yellow solutions, the colour of which became deeper on heating but faded again on cooling, explained the change by the formation of a biradical (VI). A similar explanation has been advanced for the reversible colour change of dixanthylen (compare VII) and other ethylenes exhibiting thermochromism (Schönberg and Schütz, *loc. cit.*; Schönberg, Kaltschmidt, and Schulten, *Ber.*, 1933, **66**, 247; Bergmann and Corte, *loc. cit.*).



(VIII; two structures.)



(IX.)

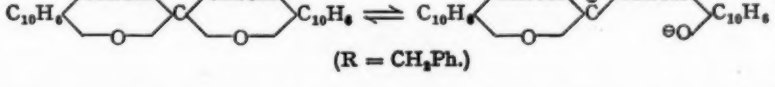
Ethylene–Betaine Theory.—The following hypothesis is now advanced, which explains not only the above-mentioned colour changes by the action of heat and pressure, but also the remarkable chemical properties of these substances and connects these phenomena with facts known in other fields of chemistry.

It is suggested that these substances are true ethylenes in the crystalline state, especially at low temperatures, as indicated by the formulæ (I*a*)—(V), but in the melt and in hot solutions the molecules acquire the structure of betaines, those of (III) and (I*a*) being written as (VIII) and (IX), respectively.

It is more correct to state that the molecules of dixanthylen (III) and of related substances are to be regarded as resonance hybrids with contributions *inter alia* from the true ethylene structure and the betaine structure, and that when the substances are molten or in hot solution there is a large contribution to the mesomeric state from the latter structures and a relatively small contribution from the true ethylene form. The reverse is the case with the molecules of the *crystallised* dixanthylen and of the other thermochromic ethylenes, especially at low temperatures.

A similar explanation is proposed to explain the above phenomenon of piezochromism. It should be noted that the colour obtained by pressure is of the same shade as that of the melt or of hot solutions.

The colour changes of the above ethylenes may be compared with those of certain *spiro*-compounds (Löwenbein and Katz, *Ber.*, 1926, **59**, 1377; Dickinson and Heilbron, J., 1927, 14; Dilthey and Wübken, *Ber.*, 1928, **61**, 963), which have also been explained by the formation of betaines as illustrated below:



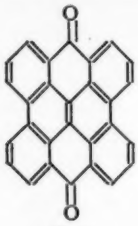
(R = CH_2Ph.)

The above *spiro*-compound forms colourless crystals which become blue on melting; the solution in hot xylene is deep blue, and on cooling it becomes paler and finally colourless (Löwenbein and Katz, *ibid.*, p. 1382).

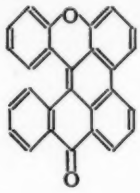
The betaine structures of the ethylenes (I*a*)—(V) may be divided into two groups of which (VIII) and (IX) are representative and show the principal difference. In (VIII) the atom of the highest electron density is a carbon atom, whereas in (IX) it is a hetero-atom. To the former group belong (III), (IV), and (V) and the sulphur analogues of (III) and (IV), and to the latter group belong (I*a*), (I*b*), (II*a*), and (II*b*). Each of the two groups shows remarkable chemical properties.

Photochemical Reactions.—Three of the substances belonging to the latter group, *viz.*, (I*a*), (II*a*), and (II*b*), are easily dehydrogenated under the influence of light, and a new condensed ring system is formed. This remarkable reaction occurs only with these compounds, and takes place in the case of (II*a*) (Meyer and co-workers, *Monatsh.*, 1912, **33**, 1465) and (II*b*) by the action of sunlight filtered through glass, but in the case of (I*a*) by the action of ultra-violet light (Clar, *Ber.*, 1930, **63**, 869). The reaction products obtained are

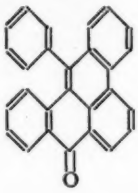
respectively (X), (XI) (the name " oxapenenon " is given to this *substance*), and (XII); (XI) forms red crystals, in contrast to helianthrone (XIII) which is blue and (II*a*) which is yellow.



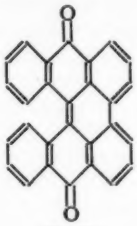
(X.)



(XI.)

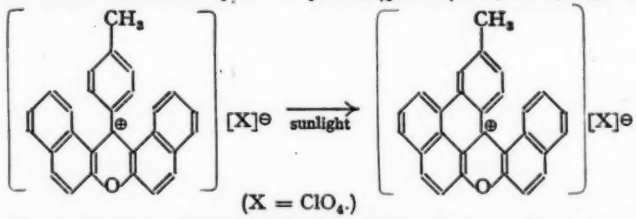


(XII.)



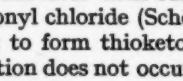
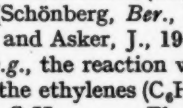
(XIII.)

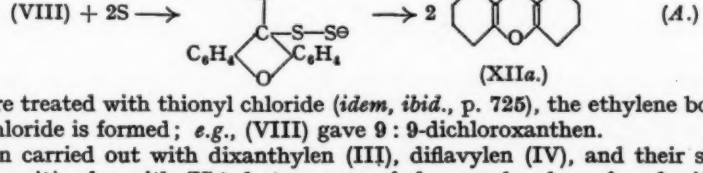
There is no process strictly analogous to this photo-dehydrogenation, in which hydrogen atoms directly attached to an aromatic nucleus play a rôle, except among betaines or salts; for salts (which are closely related to betaines) similar reactions are described by Dilthey and Quint (*Ber.*, 1936, **69**, 1584):



(X = ClO_4.)

We suggest that, in these reactions of diphenylmethyleneanthrone (I*a*) and related substances, the light should be considered as acting, not on the ethylenes, but on the betaines, and this makes the similarity between the cases of (I*a*), (II*a*), and (II*b*) and those described by Dilthey more striking.

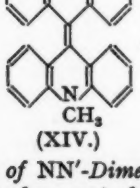
Sulphur and Thionyl Chloride Cleavage.—Substances (III), (IV), their sulphur analogues, and (V) * show very remarkable behaviour with sulphur (Schönberg, *Ber.*, 1925, **58**, 1796; Schönberg and Asker, *loc. cit.*), as well as with thionyl chloride (Schönberg and Asker, J., 1942, 725). When heated with elementary sulphur they rapidly react to form thioketones; *e.g.*, the reaction with dixanthylen takes place in a few minutes at 290°. As this reaction does not occur with the ethylenes $(C_6H_4R)_2C{:}C(C_6H_4R)_2$, where R = H, *p*-OMe, *p*-NMe_2, or *p*-C_6H_5, or with  or  (*idem*, *ibid.*, p. 272), it is believed that the cleavage should be described as the action of sulphur on a betaine, as formulated in (*A*).



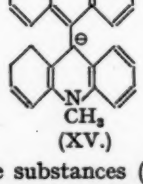
(XII*a*.) (*A*.)

When the ethylenes are treated with thionyl chloride (*idem*, *ibid.*, p. 725), the ethylene bond is broken and the corresponding keto-chloride is formed; *e.g.*, (VIII) gave 9 : 9-dichloroxanthen.

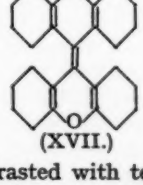
This reaction has been carried out with dixanthylen (III), diflavylen (IV), and their sulphur analogues (Schönberg and Asker, *loc. cit.*), also with (V)*, but no case of cleavage has been found with substances not closely related to these. It is believed, for the reason explained above (compare scheme A), that the thionyl chloride reacts with the betaine form.



(XIV.)



(XV.)

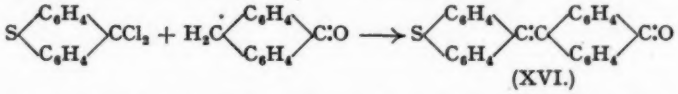


(XVII.)

Constitution of NN′*-Dimethyldiacridine.*—The substances (I*a*)—(V) may be contrasted with tetraphenylethylene, which does not show the phenomenon of thermochromism or piezochromism or undergo photo-dehydrogenation or react with elementary sulphur or thionyl chloride in the manner described above. On the other hand, dixanthylen and diflavylen may be compared with *NN′*-dimethyldiacridine (XIV) which shows cleavage with sulphur (Gleu and Schaarschmidt, *Ber.*, 1939, **72**, 1246) and with thionyl chloride (Schönberg and Asker, *loc. cit.*, p. 725). The deep colour of the substance at room temperature makes it probable that it should be described as a betaine (XV), which should be compared with (VIII).

These phenomena require investigation by modern physical methods, but a review of the organic chemistry is given by Schlenk (" Ausführliches Lehrbuch der organischen Chemie," 1939, II, 626).

Special Part.—When the keto-chlorides of 4 : 4′-dimethoxybenzophenone, xanthone, and thioxanthone are allowed to react with anthrone in dry xylene, dianisylmethyleneanthrone (I*b*), 10-(9′-xanthylen)anthrone (II*b*), and 10-(9′-*thioxanthylen*)*anthrone* (XVI), respectively, are obtained, *e.g.*,



(XVI.)

These reactions are similar to the formation of diphenylmethyleneanthrone (I*a*) by interaction between benzophenone keto-chloride and anthrone (Padova, *loc. cit.*). The presence of one carbonyl group in (II*b*) was ascertained by its reaction with phenylmagnesium bromide, followed by hydrolysis in the usual manner, whereby 9-*phenyl*-10-(9′-*xanthylen*)-9 : 10-*dihydroanthranol* (XVII) was formed; it is a light yellow substance which gives strong halochromy with concentrated sulphuric acid.

When the light yellowish-green compound (XVI) in benzene solution is illuminated with direct sunlight, it forms a deep red solution showing an intense green fluorescence.

Experimental.

Dianisylmethyleneanthrone (I*b*).—4 : 4′-Dimethoxybenzophenone (11 g.) and oxalyl chloride (10 g.) were mixed and heated under reflux for 3 hours; the excess of oxalyl chloride was driven off under vacuum. The residue (4 : 4′-dimethoxydiphenyldichloromethane; Straus and Dützmann, *J. pr. Chem.*, 1921, **103**, 46) was dissolved in dry xylene (30 c.c.; sulphur-free), and the mixture dropped slowly into a solution of anthrone (8·8 g.) dissolved in dry xylene (35 c.c.); an immediate evolution of hydrogen chloride occurred and the solution became darker and finally reddish-brown. After the addition was complete, the mixture was refluxed for two hours, then cooled; the brown precipitate formed was filtered off and treated with boiling acetone (100 c.c.); the acetone solution was filtered while hot and the filtrate treated with acidulated water, whereupon a brown crystalline precipitate separated (12 g.). *Dianisylmethyleneanthrone* (I*b*), crystallised from acetone (animal charcoal) and repeatedly from glacial acetic acid, formed shining canary-yellow crystals, m. p. 190° (ruby-red melt). It gave an intense violet coloration with concentrated sulphuric acid. It is soluble in cold anisole with an orange-red colour (Found : C, 82·9; H, 5·4. $C_{29}H_{22}O_2$ requires C, 83·2; H, 5·3%). When pressed strongly with a glass pestle, the crystals attained a permanent orange-red colour, which changed back to yellow when they were subjected to ether vapour.

10-(9′-*Xanthylen*)*anthrone* (II*b*).—Xanthone (10 g.) was dissolved in thionyl chloride at room temperature and heated under reflux for 10 hours. The thionyl chloride was then distilled off under vacuum, and the residue treated with dry xylene (70 c.c.). The mixture was dropped slowly into a boiling solution of anthrone (10 g.) in dry xylene (35 c.c.); an immediate evolution of hydrogen chloride occurred and the solution gradually became deep green. After the addition was complete, the mixture was heated under reflux for 12 hours, evolution of hydrogen chloride then being complete. The product was cooled in ice, the deep green crystalline precipitate filtered off (10 g.), boiled for about 15 minutes with glacial acetic acid (200 c.c.), and filtered off while hot. The insoluble part was crystallised once from acetylene tetrachloride and then repeatedly from benzene–ligroin (b. p. 45—75°), forming yellowish-green crystals, m. p. 301—302°, giving a deep green melt with slight sublimation (Found : C, 86·6; H, 4·4. $C_{27}H_{16}O_2$ requires C, 87·0; H, 4·3%). 10-(9′-*Xanthylen*)*anthrone* gave a yellowish-green coloration with concentrated sulphuric acid. The crystals became deep green on pressing, the colour being restored by ether vapour. They show reversible and pronounced thermochromic effects in very dilute solutions, *e.g.*, in benzonitrile, anisole, or xylene.

10-(9′-*Thioxanthylen*)*anthrone* (XVI).—Thioxanthone (8 g.) (Gomberg and Britton, *J. Amer. Chem. Soc.*, 1921, **43**, 1946) was dissolved in thionyl chloride at room temperature and heated under reflux for ten hours. The thionyl chloride was then distilled off under vacuum, and the residue treated with dry xylene (100 c.c.) and then with anthrone (7·8 g.), evolution of hydrogen chloride occurring; after 15 minutes at room temperature, the mixture was heated under reflux for 12 hours, the evolution then being complete. The mixture was allowed to cool to room temperature, left for ½ hour, and filtered from the dark resin. The dark brown filtrate was concentrated under reduced pressure to about 50 c.c., cooled, and the very dark precipitate filtered off; a further quantity was obtained from the mother-liquor by slow concentration to about 20 c.c. The combined crops were triturated with ether (50 c.c.) and separated (yield about 6 g.). Repeated crystallisation from benzene afforded 10-(9′-*thioxanthylen*)*anthrone* (XVI) as greenish-yellow crystals, m. p. 308°. It showed no thermochromic effects in benzonitrile, anisole, or xylene and gave a deep reddish-violet coloration with concentrated sulphuric acid (Found : C, 83·0; H, 4·2; S, 8·1. $C_{27}H_{16}OS$ requires C, 83·5; H, 4·1; S, 8·2%).

Action of Phenylmagnesium Bromide on 10-(9′-*Xanthylen*)*anthrone* (II*b*).—To an ethereal solution of phenylmagnesium bromide, prepared from magnesium (0·73 g.), bromobenzene (4·7 g.), and dry ether (20 c.c.), dry benzene (100 c.c.) was added, and the hot solution treated gradually with powdered (II*b*) (3·7 g.). The ether was evaporated slowly and refluxing continued with stirring for 3 hours. The product was cooled, then decomposed with ammonium chloride and ice, and the benzene layer separated, washed with water, and dried over anhydrous sodium sulphate. The benzene solution was evaporated to dryness and the deep green oily residue solidified after two days. 9-*Phenyl*-10-(9′-*xanthylen*)-9 : 10-*dihydroanthranol* (XVII) crystallised from acetone (1·1 g.) then from acetone–alcohol as light yellow crystals, m. p. 255° giving a dark melt. It gave a deep bluish-green coloration with concentrated sulphuric acid (Found : C, 87·4; H, 5·0; active H, 0·24. $C_{33}H_{22}O_2$ requires C, 87·9; H, 5·0; active H, 0·22%).

Photochemical Experiments.—The experiments were carried out in Monax glass tubes, the air being displaced by dry carbon dioxide and the tube sealed by fusion. The benzene used was thiophen-free (Kahlbaum) and dried over sodium.

(A) 10-(9′-Xanthylen)anthrone (II*b*) (1 g.) was dissolved in benzene (25 c.c.) and left in direct sunlight for one week (June); the solution became red with an intense green fluorescence, and on concentration to 5 c.c. under reduced pressure and cooling, it afforded crystals of *oxapenenon* (XI) (0·5 g.); this crystallised from benzene as red crystals, m. p. 245—246° (Found : C, 87·0; H, 3·8. $C_{27}H_{14}O_2$ requires C, 87·5; H, 3·8%). It gave a malachite-green coloration with concentrated sulphuric acid. It is sparingly soluble in cold and hot alcohol with an orange-red colour and a yellow fluorescence, the fluorescence being more intense in the cold. It dissolves in cold benzene with a yellowish-green fluorescence. When a drop of the benzene solution was put on a glazed white porcelain plate, it looked bright yellow without any red coloration, but it dried to orange red crystals.

(B) *Action of sunlight on* 10-(9′-*thioxanthylen*)*anthrone* (XVI). The compound (1 g.) was dissolved in benzene (25 c.c.) and left in direct sunlight for two weeks (July); the colour of the solution became red with green fluorescence, but the compound was only obtained as a red oil which gave an intense green coloration with concentrated sulphuric acid.

Action of Sulphur on Diphenylmethylenexanthen (V) *.—The substance (Schönberg and Mustafa, J., 1944, 67) (1 g.) was ground with sulphur (1 g.) and heated gradually in a paraffin-bath. At 140° the mixture melted and became orange-coloured; this colour remained up to 270°, and then changed immediately to green. After 10 minutes, the melt was allowed to cool, powdered, and extracted with benzene. The extract was concentrated, cooled, filtered from sulphur, concentrated again, and cooled; green crystals were obtained, m. p. 156°, not depressed by admixture with authentic xanthione (XII*a*) (Schönberg and co-workers, *Ber.*, 1928, **61**, 1382).

Action of Thionyl Chloride on (V) *.—The substance (0·5 g.) was dissolved in thionyl chloride (yellow solution) and heated under reflux on a water-bath for 3 hours. The excess of thionyl chloride was distilled off under reduced pressure, and the residual orange oil was dissolved in benzene (20 c.c.) and shaken with water (10 c.c.). The benzene layer was isolated and evaporated; the yellow substance obtained was extracted with ligroin (b. p. 30—50°). After evaporation, colourless crystals were obtained, m. p. 49°, not depressed by admixture with authentic benzophenone. The residue was then extracted with ligroin (b. p. 100—110°) from which xanthone was obtained, m. p. 174°, not depressed by admixture with an authentic specimen.

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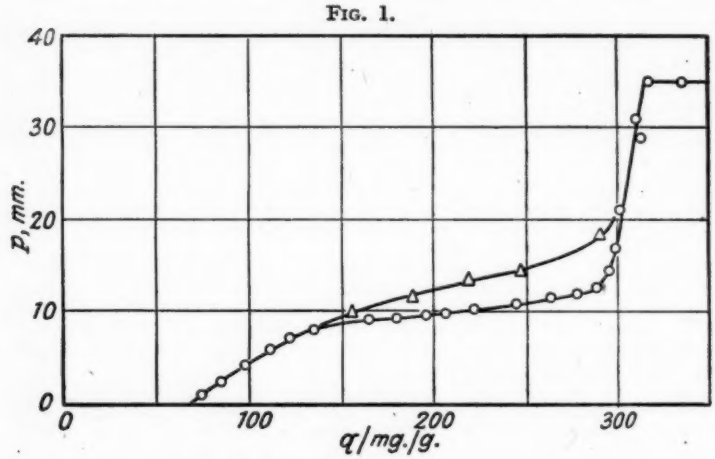
84. *The Sorption of Vapours by Ferric Oxide Gel. Part II.*

By D. W. BROAD and A. G. FOSTER.

Sorption isothermals of the following substances on ferric oxide gel have been determined: carbon tetrachloride, chloroform, *cyclo*hexane, dioxan, ethyl iodide, *n*-hexane, morpholine, *n*-octane, di*iso*propyl ether, toluene and triethylamine. All show an intermediate linear range followed by a large hysteresis area. The results are in general agreement with the capillary theory, since the pore radius of the adsorbent calculated by means of the Kelvin equation remains reasonably constant. The application of the theory of multimolecular adsorption and its possible bearing on hysteresis phenomena is also discussed.

IN Part I (*Proc. Roy. Soc.*, 1934, *A*, **147**, 128) isothermals of the alcohols from methyl to *n*-butyl were described, following earlier work by Lambert and Clark (*ibid.*, 1929, *A*, **122**, 497) with benzene. Isothermals of D_2O and H_2O on ferric oxide have recently been determined by the authors (J., 1945, 372) who also examined the sorption of a large number of vapours by silica gels (*ibid.*, p. 366). This paper describes isothermals of these substances on a new batch of ferric oxide gel, prepared according to the instructions of Lambert and Clark (*loc. cit.*).

FIG. 1.



The results obtained in the earlier investigations may be summarised as follows. On silica gel B, constant volumes are adsorbed at saturation, q, the weight adsorbed, being proportional to d, the density of the liquid. The amount (z) held in the unimolecular layer corresponds to the covering of a constant surface area, since $z\sigma^2/M$ is constant, σ being the molecular diameter. Neither of these simple relations holds for silica gel A, where both q/M and $z\sigma^2/M$ are functions of σ. On ferric oxide the amounts of the various alcohols held in the unimolecular layer correspond to a constant number of molecules, but this is still consistent with a constant surface area if it is assumed that the molecules are oriented perpendicularly to the surface. The capillary radii (calculated by means of the Kelvin equation from the pressure at the point of inflexion in the desorption curves) remain constant.

In the present work, attention has been directed mainly to the following objects: (i) calculation of the capillary radius, (ii) determination of the amounts held in the unimolecular layer. The former requires an accurate determination of the course of the descending branch of the hysteresis loop in order that the point of inflexion may be accurately located. The latter is effected by a method recently described by one of us (Foster, J., 1945, 773) in which the linear middle part of the isothermal is extrapolated back to zero pressure. The descending branch of the hysteresis loop and the linear portion of the isothermals have therefore been investigated in detail, whilst the ascending branch has in many cases not been examined. The absence of extensive data at lower pressures, before the linear range begins, is due to the fact that the pressures were too low to be measured accurately on a mercury manometer. Some low-pressure measurements with the Pirani gauge have been described recently (Foster, J., 1945, 360).

EXPERIMENTAL.

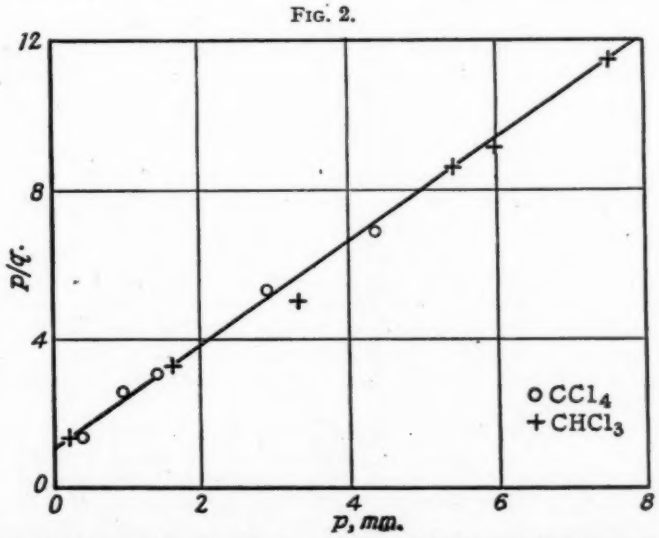
The experimental technique was described in Part I. The isothermals were determined at 25° except those for chloroform and hexane which were investigated at 20°. A typical isothermal, that for dioxan, is reproduced in Fig. 1,

but owing to the importance of accurate comparative data for testing rival theories of adsorption, the remaining results are recorded in tabular form. In Table I, concentrations (q) are expressed in mg./g. of gel, and pressures (p) in mm. of

TABLE I.

Carbon tetrachloride.															
q	400	387	376	365	354	345	334	323	313	303	292	282	272	262	253
p	53·9	48·0	45·4	43·8	42·8	42·2	41·7	41·2	40·4	39·7	39·1	38·5	38·4	37·9	37·4
q	244	234	225	215	206	197	181	166							
p	36·6	36·6	35·5	34·2	33·9	32·1	29·4	25·9							
Chloroform.															
q	409	371	335	300	266	234	204	179	158	141	127	116	108	102	97
p	102	70·7	68·2	65·3	63·0	58·9	55·1	48·0	41·5	34·4	27·4	21·8	17·3	14	11·7
q	93	89	54		Ascending points	q	185	277							
p	9·6	8·2	1·5			p	55	77							
***cyclo*Hexane.**															
q	224	204	186	169	153	138	123	111	100	90	81	73	67	57	50
p	74·6	40·1	35·9	34·3	33·0	31·6	29·9	28·3	26·1	23·4	21·2	18·3	15·7	11·9	8·7
q	45														
p	6·6														
Ethyl alcohol.															
q	232	217	201	178	155	117	102	98	77	70	66	61			
p	46·7	38·6	37·5	36·3	35·6	33·9	32·3	30	24	16	8·3	2·5			
Ethyl iodide.															
q	525	498	472	447	423	400	354	312	275	241	211	187	151	121	109
p	92·4	65·5	62·8	60·9	59·6	57·8	55·2	52·2	48·5	43·7	37·9	31·7	20·0	9·4	5·2
q	86	72			Ascending points	q	237	270	305	363					
p	1·3	0·3				p	46	52	61	68					
***n*-Hexane.**															
q	195	187	178	168	160	150	141	131	122	105	93	83	74	68	63
p	89	59	48·5	45·3	45	43·7	42·5	40·8	39·3	35·9	29·5	23·3	18·1	14·1	11·1
q	59	56	51	47	36	23									
p	8·8	7·3	5·4	4·1	1·3	0·4									
***n*-Octane.**															
q	192	189	185	181	161	130	124	117	108	100	91	86	74	66	48
p	11·5	7·2	4·3	3·8	3·6	3·3	3·2	3·1	2·9	2·8	2·6	2·4	1·8	1·4	0·5
Di*iso*propyl ether.															
q	210	185	165	143	138	123	117	100	87	77	66	60	56	51	
p	99·3	56·3	52·0	49·6	49·3	47·1	45·2	37·5	29·3	21·1	12·9	7·9	4·5	1·5	
Toluene.															
q	227	222	211	201	191	172	154	136	120	106	94	78	71		
p	11·0	10·3	9·6	9·3	9·1	8·5	8·0	7·6	7·0	6·2	5·0	3·7	3·0		
Triethylamine.															
q	226	213	200	192	181	163	146	130	109	102	96	85	66	56	
p	54	28·7	24	23	22·3	21·1	20	18·9	16·9	16·0	14·7	11·4	5·0	1·8	

FIG. 2.



mercury at the temperature of the experiment. The lower part of the hexane isothermal has already been described (Foster, J., 1945, 774) in illustrating the method of estimating the saturation value for unimolecular adsorption. The lowest points on the isothermals of carbon tetrachloride and chloroform give linear plots of p/q against p in agreement with the Langmuir equation. These curves, which happen to coincide, are shown in Fig. 2, and follow the relation

$p/q = 0{\cdot}010 \pm 0{\cdot}014p$, according to which the saturation value is 1/0·014 or 71·5, agreeing well with the value of 72 extrapolated from the linear range.

Discussion.

Table II summarises the more important data for the systems examined, including some figures for benzene, which was re-investigated for comparative purposes. Col. 2 gives the saturation volumes and col. 3 the number

Table II.

Substance.	Saturation vol. (mm.³/g.).	$10^5 . z/M$ (moles/g.).	$10^4 . z\sigma^2/M$.	r (A.).	$r + 2\sigma$.
Benzene	281	49	164	19·0	31·0
Carbon tetrachloride	270	48	179	19·0	31·0
Chloroform	282	62	205	20·5	32·0
*cyclo*Hexane	295	38	152	20·0	32·5
Deuterium oxide	306	275	340	19·0	26·0
Dioxan	302	74	258	19·0	31·0
Ethyl alcohol	300	125	337	20·5	31·0
Ethyl iodide	295	62	204	21·0	32·5
n-Hexane	308	52	239	18·5	32·0
Morpholine	282	77	268	19·5	31·0
n-Octane	278	35	187	20·0	34·5
Di*iso*propyl ether	290	47	230	18·0	32·0
Toluene	272	49	164	19·5	32·0
Triethylamine	300	50	238	18·0	32·0
Water	302	280	342	19·0	26·0

of moles required to saturate the unimolecular layer, determined by extrapolation as already mentioned. The saturation volumes are not absolutely constant, but the fluctuations (which are far beyond experimental error) do not seem to depend on the diameter (σ) of the adsorbed molecule, in which respect ferric oxide gel appears to resemble the silica gel B rather than the gel A investigated by the present authors. On these silica gels it was found that z/M was a linear function of $1/\sigma^2$, but no such simple relation holds here, since col. 4 shows that the values of $z\sigma^2/M$, which should be constant for the covering of a constant surface area, vary from 0·0152 to 0·0342, nor is it possible to draw a smooth curve through the plot of z/M against $1/\sigma^2$. It will be seen that approximately twice as many molecules of dioxan as of *cyclo*hexane are held in the first layer, in spite of the similarity of size and shape. The maximum value of $z\sigma^2/M$ is 0·0342 for water, the smallest molecule, but the lowest values (0·0152—0·0179) are not associated with the largest molecules. It must, however, be remembered that the value of σ calculated from the density of the liquid is only an average value and no assumptions as to the orientation of the adsorbed molecules have been made. The work of Herington and Rideal (*Trans. Faraday Soc.*, 1944, **40**, 505) on the poisoning of metallic catalysts suggests a possible reason for some of the low adsorption values. If a hexagonal molecule, in order to be adsorbed, needs to be attached at all corners to fixed points in the lattice, the surface will never be completely covered, and even at saturation, about 35% will be bare, according to their calculations. Presumably a hexagonal molecule with a polar group like the oxygen atom in dioxan can attach itself more readily.

From the pressure–concentration data it is possible to construct " radius–volume " curves by application of the Kelvin equation as previously described (Foster, *Trans. Faraday Soc.*, 1932, **28**, 645). These r–v curves have a point of inflexion, which can be located by drawing tangents, at which dv/dr reaches a maximum similar to that of the Gauss error function. The value of r at this point corresponds to the radius of the most frequently occurring pores of the adsorbent, so that by determining the point of inflexion of the r–v curve we can define fairly sharply ($\pm$ 0·5A.) an " average radius " which would be characteristic of a given adsorbent if the adsorbed layer did not vary in thickness. The r values obtained in this manner, tabulated in col. 5, show quite good agreement, but must actually be less than the true pore radius. Since the amounts held in the unimolecular layer are about half those held when hysteresis begins, it has been assumed that the adsorbed layer is two molecules thick, so that the values of $r + 2\sigma$ should represent the true radius of the capillaries and therefore be constant. As shown in col. 6, the agreement is good except for water and *n*-octane, but since the hysteresis loop of the water isothermal does not begin until 120 mg./g. have been adsorbed, and the first layer is saturated at about 40 mg./g., it would not be unreasonable to assume that the adsorbed layer is at least three molecules thick by the time condensation begins, which would make $r + 3\sigma = 29{\cdot}5$ A. A long-chain molecule like *n*-octane would probably tend to lie flat on the surface, and if a value of 5 A. is assumed for the " width " of the hydrocarbon chain, $r + 2\sigma$ is approximately 30 A.

In view of the somewhat divergent values reported by different workers for the physical constants of some of the liquids investigated, it was thought desirable to record the values actually used for calculating the capillary radii. The surface-tension data of Table III are mainly from the extensive series of measurements carried out by Hennault, Roland, and Lek (*Chem. Abs.*, 1931, **25**, 5322) and a re-calculation of the capillary radii from the alcohol isothermals described in Part I has been made, using these data instead of the earlier figures of Ramsay and Shields, which, as pointed out by Sugden (" The Parachor and Valency," London, 1930), are subject to a meniscus correction. Values marked with an asterisk were determined by us where no data could be found in the literature. Surface tensions were determined in a vacuum by the capillary-rise method.

TABLE III.

Physical constants of adsorbed liquids at 25°.

	d.	*γ.*	V. p. (mm. Hg).		*d.*	*γ.*	V. p. (mm. Hg).	*r* (A.).
Carbon tetrachloride ...	1·584	26·16	115	Alcohols :				
Chloroform (20°)	1·489	27·28	160·5	Methyl	0·787	22·12	116	22·0
*cyclo*Hexane	0·773	24·40	96	Ethyl	0·785	21·90	59	20·0
Dioxan	1·028	34·69	35·5	*n*-Propyl	0·799	23·30	21·2	23·5
Ethyl iodide	1·93	28·22	135	*iso*Propyl	0·781	20·90	43·7	22·0
n-Hexane (20°)	0·660	18·42	122·5	*n*-Butyl	0·806	24·16	6·75	23·5
n-Octane	0·699	21·25	14·0					
Di*iso*propyl ether	0·719	17·01 *	149·3 *					
Toluene	0·862	27·96	28·9					
Triethylamine	0·726	20·67 *	74·1 *					
Water	0·997	72·7	23·75					

The isothermals of benzene on ferric oxide described by Lambert and Clark (*loc. cit.*) have been interpreted in a rather different manner by Brunauer, Deming, Deming, and Teller (*J. Amer. Chem. Soc.*, 1940, **62**, 1723) who modified the earlier multilayer theory (Brunauer, Emmett, and Teller, *ibid.*, 1938, **60**, 309) in an attempt to include capillary condensation. The last adsorbed layer closes the capillary or cavity and causes a considerable decrease in the exposed surface of the adsorbed liquid, which is accompanied by considerable evolution of heat, shown by the rise in the heat of sorption just before saturation. It is therefore assumed that the constant c of the general equation [see Foster, J., 1945, p. 770, equation (1)] has a higher value for the last layer than for the intermediate layers, since the net heat of sorption is no longer zero. Brunauer *et al.* (*loc. cit.*, 1940) assume that the heat evolved is equal to the decrease in free energy and hence is determined by the product of the surface area and the surface tension (γ), but actually the differential heat effect accompanying a change of surface is determined by the total surface energy ($\gamma - T.\mathrm{d}\gamma/\mathrm{d}T$) and not the free surface energy (γ) (cf. Lewis and Randall, " Thermodynamics," p. 249). The predicted rise in the heat of sorption just before saturation is a well-known characteristic of layer adsorption, as pointed out by Kruyt and Moddermann (*Chem. Reviews*, 1930, **7**, 320) and illustrated by the results of Goldmann and Polanyi (*Z. physikal. Chem.*, 1928, *A*, **132**, 313). On the other hand, according to Hückel (*Trans. Faraday Soc.*, 1932, **28**, 138), the capillary theory requires the heat of sorption to remain constant during condensation in pores of uniform radius. The use of an increased value for c for the last layer can therefore hardly be regarded as an adequate mode of including capillary condensation, and must be considered merely as an arbitrary method of making the isothermals assume the desired shape.

The exceedingly complex equations, to which the modified multimolecular theory finally leads, were found by Brunauer *et al.* to give reasonable agreement with the experimental curves of Lambert and Clark (*loc. cit.*) when suitable values were assigned to the various constants. The amount required to saturate the first layer was taken as 81 mg./g. compared with 48—50 mg./g. estimated by Foster (J., 1945, 775); the number of adsorbed layers was assumed to be 3, whereas the capillary theory requires 5—6, and finally, the net heat of sorption was supposed to fall to zero after the formation of the first layer and to rise to 1690 cals./mole for the last, whereas the " observed " value (calculated by means of the Clapeyron equation) remains quite constant at 780 cals. over the latter half of the sorption process. The multimolecular theory thus assumes a pore radius so small that one could not expect the Kelvin equation to hold, whereas in fact excellent agreement is observed with this equation. The layer theory also predicts a rise in the heat of sorption which is non-existent, and suffers from the additional drawback that, unlike the capillary theory, it provides, by itself, no explanation of the hysteresis phenomena. It is noteworthy that the sorption of benzene on silica gel, which was also investigated by Lambert and Clark (*loc. cit.*), does actually show the predicted rise in heat of sorption just before saturation, but there is no evidence that capillary condensation takes place on this gel, and later work by the present authors (J., 1945, 366) indicates that it contains no pores wider than 10 A.

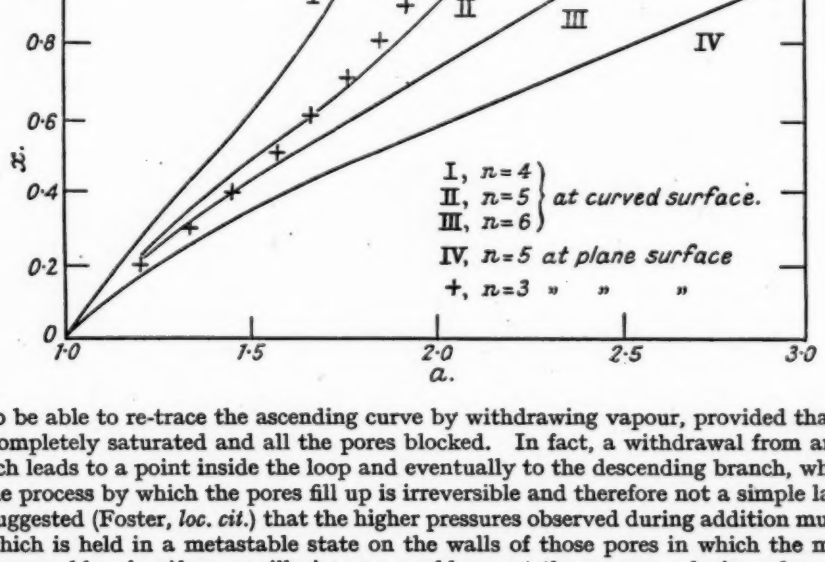
The claim that the extended multilayer theory includes capillary condensation is thus hardly justified, and the theory should be regarded as an attempt to develop a more accurate picture of layer adsorption rather than as a new or modified capillary theory, since the only capillary effect which it considers is that which necessarily accompanies the last stage of layer adsorption in any closed space. When true condensation occurs the decrease in free surface takes place gradually as the pores fill and the associated heat effect is determined by the pore radius.

A further defect in the multilayer theory, admitted by the authors, is the assumption that the walls of the cavities are parallel, and therefore that the same area is available for the formation of the last layer as for the first. Obviously in a cylindrical pore the surface of successive layers falls off in an arithmetical progression, and if the relative diameters of the capillary and the adsorbed molecule are known, an exact correction can be applied. Suppose, for example, that five layers will just fill a cylindrical capillary, then the volumes of the first and second layers, respectively, will be in the ratio $(5^2—4^2) : (4^2—3^2)$ or 9 : 7, and the volumes occupied by the five layers when completely filled would be in the ratio 9 : 7 : 5 : 3 : 1. The ratio of the total adsorption volume to that of the first layer will thus be reduced to 25 : 9 compared with 5 : 1 at the plane surface. In calculating the total adsorption (a) at the latter, the fraction (s_n) covered by n layers is counted n times, *e.g.*, $a = s_1 + 2s_2 + 3s_3 + 4s_4 + 5s_5$. For the cylindrical pore we must replace the factor 2 by $(9 + 7)/9$ and the

factor 3 by $(9 + 7 + 5)/9$ and so on, giving the total sorption as $a = s_1 + \frac{16}{9}s_2 + \frac{21}{9}s_3 + \frac{24}{9}s_4 + \frac{25}{9}s_5$. Similar relations can be derived for systems of different relative dimensions, and when introduced into the general equations of the multilayer theory will cause the isothermals to rise more steeply than the corresponding curves for a plane surface, as shown in Fig. 3 where the curves for adsorption in pores of radii 4, 5, and 6 times the diameter of the adsorbed molecule are compared with those for 3 and 5 layers on a plane surface.

As already mentioned, little attention has been paid to the hysteresis phenomena in this work, but it has been established that on ferric oxide gel, in contrast to silica gel, there is no significant variation in the size of the hysteresis loop with the size of the adsorbed molecule. It has been pointed out (Foster, *Trans. Faraday Soc.*, 1932, **28**, 647) that over the " ascending " branch the adsorption potential at constant volume is independent of temperature, in agreement with the older " potential " theory of multilayer adsorption (Polanyi, *Verh. deut. physikal. Ges.*, 1916, **18**, 55), whereas, during desorption, the potential is determined by the Kelvin equation. It is therefore noteworthy that the attempt made by Brunauer *et al.* to apply the new multilayer theory to the benzene isothermals gave a curve which, over the hysteresis loop, followed the " ascending " and not the " descending " branch, so that the pores appear to fill up in accordance with the multimolecular theory and to empty in accordance with the capillary theory. The logical conclusion is that, during adsorption, the pores fill by layer formation, the adsorbed layer gradually extending further outward from the walls until it fills the entire pore space and the pores are blocked in the middle by the formation of the last layer. During desorption the pores empty from the top downwards, leaving an adsorbed layer about two molecules thick on the walls. This, however, would not completely account for the behaviour of systems in the hysteresis area, since one

FIG. 3.



would expect to be able to re-trace the ascending curve by withdrawing vapour, provided that the adsorbent had not been completely saturated and all the pores blocked. In fact, a withdrawal from any point on the ascending branch leads to a point inside the loop and eventually to the descending branch, whence it must be inferred that the process by which the pores fill up is irreversible and therefore not a simple layer adsorption.

It has been suggested (Foster, *loc. cit.*) that the higher pressures observed during addition must be attributed to the liquid which is held in a metastable state on the walls of those pores in which the meniscus has not formed. In an assembly of uniform capillaries one would expect the pressure, during adsorption, to remain abnormally high until enough liquid had accumulated on the walls to enable the meniscus to form, then to drop abruptly to the descending curve. In any actual assembly of non-uniform pores, the narrower capillaries will fill before the wider, so that there will always be some pores blocked and some open. The pressure over the former would be determined by the Kelvin equation, and over the latter by the multimolecular theory. The liquid held on the walls at the higher pressure cannot distil into the pores over which the lower pressure prevails because the latter are either filled completely, or would, by further condensation, be filled to a larger radius, where the pressure would be higher. It must therefore remain on the walls until enough accumulates to block the pores by forming a meniscus, but meanwhile, a similar process will be repeating itself in the next larger set of pores, and until all the pores have been filled, the layer adsorption continues to mask the condensation process. Naturally, if layer adsorption takes place at a lower pressure than capillary condensation, no hysteresis should be observed. For this reason, the development of a more exact theory of multimolecular adsorption, in cylindrical pores rather than at a plane surface, would be of considerable importance in elucidating the mechanism of hysteresis. Some of the factors which determine the size of the hysteresis loop will be discussed in a later paper.

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85. *Compounds Related to Penicillic Acid. Part I. Ethyl β-Propionylacrylate and its Formylation Product.*

By J. S. Moffatt, G. Newbery, and W. Webster.

The synthesis of *ethyl β-propionylacrylate* by three different routes is described. Of these, the most satisfactory for preparative purposes was the esterification of *β-propionylacrylic acid*, obtained by the acid hydrolysis of *ethyl propionyl-fumarate* (or *-maleate*), which is the product of condensation between ethyl hydroxyethoxyacetate and ethyl propionylacetate. Formylation of ethyl β-propionylacrylate yielded a product which could not be purified but which, from its properties, and by analogy with the successful formylation of ethyl propionylfumarate (or -maleate) also described, would appear to consist essentially of ethyl 6-hydroxy-4-keto-5-methyl-$\Delta^{2:5}$-hexadienoate. None of these compounds showed marked bacteriostatic activity.

The antibacterial activity of the mould metabolic product, penicillic acid, to which formula (I) has been ascribed (Oxford, Raistrick, and Smith, *Chem. and Ind.*, 1942, 22), prompted an investigation of the possible antibacterial properties of a number of other compounds of similar structure. The preparation of ethyl 6-hydroxy-4-keto-5-methyl-$\Delta^{2:5}$-hexadienoate (II) was undertaken because it contains a similar system of unsaturation to that postulated for (I) as well as the hydroxymethylene grouping which occurs in other compounds of biological significance. Colchiceine, for example, as formulated by Windaus (*Annalen*, 1924, 439, 59) contains this grouping, while the mould metabolic product patulin (Raistrick *et al.*, *Lancet*, 1943, 625) appears to contain an anhydride ring formed from a carboxyl and a hydroxymethylene grouping.

(I.) $CH_3 \cdot C(CH_2) \cdot CO \cdot C(OMe) : CH \cdot CO_2H$ $\qquad$ $CH_3 \cdot C(CH \cdot OH) \cdot CO \cdot CH : CH \cdot CO_2Et$ (II.)

Ethyl β-propionylacrylate, the obvious intermediate for the preparation of (II), is not mentioned in the literature, where the only β-acylacrylic acids described appear to be benzoyl- and acetyl-acrylic acids. Of the methods previously described for the synthesis of the latter, that which seemed most likely to be applicable to the preparation of homologues was the bromination of lævulic acid, or its ester, followed by removal of hydrogen bromide from the resulting β-bromo-derivative (Wolff, *Annalen*, 1891, **264**, 246, 249). Bromination of ethyl β-propionylpropionate in ethereal solution yielded a product which appears to be mainly a mixture of monobromo-derivatives. On removal of hydrogen bromide with pyridine, this mixture gave *ethyl β-propionylacrylate* in 10% yield. The latter formed a crystalline 2 : 4-*dinitrophenylhydrazone*. As the bromination products of ethyl β-propionylpropionate have not been so far characterised, the structure of the unsaturated keto-ester thus obtained was considered ambiguous and its identity was established by its synthesis by the two methods given below.

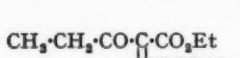
The first method involved the attempted preparation of ethyl α-bromo-β-propionylpropionate (IV) by the condensation of ethylzinc iodide with β-bromo-β-carbethoxypropionyl chloride (III). The Blaise reaction

$$\underset{\text{(III.)}}{Cl \cdot CO \cdot CH_2 \cdot CHBr \cdot CO_2Et} \xrightarrow{ZnEtI} \underset{\text{(IV.)}}{Et \cdot CO \cdot CH_2 \cdot CHBr \cdot CO_2Et} \quad \text{(A)}$$

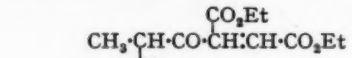
has been used by Müller and Feld (*Monatsh.*, 1931, **58**, 22) to prepare ethyl propionylpropionate from β-carbethoxypropionyl chloride, and Wohlgemuth (*Compt. rend.*, 1914, **159**, 80) describes a general method for the preparation of γ-chloro ketones from γ-chlorinated acid chlorides. On the other hand Blaise (*Compt. rend.*, 1912, **155**, 46) found that the reaction of α-chlorinated acid chlorides with organozinc halides yielded mainly the esters of chlorinated acids with chlorinated alcohols. The use of this method to prepare α- or β-halogeno-γ-keto-esters or even simple β-halogeno-ketones is not reported in the literature. In the present work it was found that, while reaction (A) proceeded quite smoothly at −20°, the required bromoketo-ester (IV) could not be isolated in a pure condition from the reaction mixture. Decomposition with elimination of hydrogen bromide occurred on attempted distillation (<1 mm.), and the crude product was accordingly treated with quinoline to remove hydrogen bromide, when an unsaturated product, stable to distillation under reduced pressure, was obtained. The latter formed a 2 : 4-dinitrophenylhydrazone identical with that mentioned above, and had b. p. and refractive index similar to those of the ethyl β-propionylacrylate obtained by the previous method. However, analysis showed that it was not pure, and it was subsequently found to consist mainly of a mixture of ethyl β-propionylacrylate and fumarate (or maleate), the b. ps. of which are so close as to preclude ready fractionation.

The following method, which should be capable of general application to the synthesis of small quantities of β-acylacrylic acids, was found more satisfactory. Ethyl hydroxyethoxyacetate (Traube, *Ber.*, 1907, **40**, 4944) was condensed with ethyl propionylacetate in presence of acetic anhydride to yield *ethyl propionyl-fumarate* (or *-maleate*) (V) which on hydrolysis and simultaneous decarboxylation with dilute hydrochloric acid gave β-*propionylacrylic acid* in 16% yield. The latter was converted into its ethyl ester by reaction of its silver salt with ethyl iodide. Formylation of ethyl β-propionylacrylate with ethyl formate in presence of sodium methoxide yielded a gum which resisted all attempts at purification. It gave a deep red colour with ferric

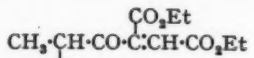
chloride, was precipitated as a copper salt on treatment with copper acetate solution, and gave analytical figures approaching those of the required formyl derivative (II).



(V.)



(VI.)



(VII.)

To ascertain whether a compound of the nature of (II) was in fact capable of existence, the formylation of the similarly constituted ethyl propionyl-fumarate (-maleate) (V) was studied. Reaction did not occur with sodium methoxide as condensing agent, but proceeded smoothly with powdered sodium. The product was a mixture of at least three components. The predominant one was an oil which distilled under high vacuum. It gave a deep red colouration with ferric chloride and analysed satisfactorily for the required *ethyl 6-hydroxy-4-keto-3-carbethoxy-5-methyl-*$\Delta^{2:5}$*-hexadienoate*. A second component, m. p. 169—170° also gave a deep red colour with ferric chloride, was soluble in sodium bicarbonate solution, and analysed for the product of a Claisen condensation of two molecules of (V); it was presumably (VI) or (VII). The third constituent, a liquid which distilled under reduced pressure, gave no colour reaction with ferric chloride, and formed a crystalline 2 : 4-dinitrophenylhydrazone, has not been identified.

The minimum dilutions at which some of these compounds showed bacteriostatic activity when tested in broth were as follows:

	M.E.D.		
	S. aureus.	*B. coli.*	*Ps. pyocyaneus.*
Ethyl 6-hydroxy-4-keto-3-carbethoxy-5-methyl-$\Delta^{2:5}$-hexadienoate	1 : 4,000	1 : 4,000	1 : 4,000
Ethyl 6-hydroxy-4-keto-5-methyl-$\Delta^{2:5}$-hexadienoate	1 : 2/4,000	1 : 2/4,000	1 : 4/8,000
Ethyl propionylacrylate	1 : 32/64,000	1 : 32/64,000	1 : 8/16,000
Propionylacrylic acid	1 : 2/4,000	1 : 2/4,000	<1 : 2,000

Experimental.

Ethyl β-Propionylpropionate.—The yield of 59% of this ester obtained by hydrolytic fission of the furan ring in 2-furylmethylcarbinol claimed by Tschitschibabin (*Chim. et Ind.*, 1932, **27**, 563 (special)) could not be substantiated; under the conditions cited, we observed much resinification with low and inconsistent yields. The somewhat modified procedure adopted, which gave consistent yields of 20—23% of pure product over several runs, was as follows. To a solution of 2-furylmethylcarbinol (60 g.) (Tschitschibabin, *loc. cit.*) in ethanol (250 c.c.), hydrochloric acid (*d* 1·16; 15 c.c.) was added in portions with shaking whereby the mixture became deep apple-green. It was heated at 63—68° (internal temperature) for 1 hour, and then boiled gently under reflux on the steam-bath for 30 minutes. Most of the alcohol, etc., was removed at 40° under reduced pressure, and the residual black oil was diluted with ether (100 c.c.) and treated gradually, with shaking, with sodium bicarbonate solution until the aqueous layer was alkaline. The mixture was filtered, the resinous residue further extracted with ether, and after separation the ethereal layer was dried ($CaCl_2$). After removal of ether the residue was distilled, b. p. 97—104°/16 mm. (yield 27·5 g.). The combined distillates from 5 similar runs were fractionated under reduced pressure. The pure ester (yield 91 g.) had b. p. 102—104°/15 mm., $n_D^{21°}$ 1·4311.

Bromination of ethyl β-propionylpropionate. A solution of ethyl β-propionylpropionate (50 g.) in dry ether (100 c.c.) was cooled to 0°, and bromine (55 g.) was slowly added with vigorous stirring, during 75 minutes. Stirring with cooling at 0° was continued for 30 minutes, after which the mixture was diluted with ether (75 c.c.), washed several times with water, shaken with charcoal, and filtered. The ether was removed under reduced pressure and the residue distilled in a high vacuum. The distillate, b. p. 70—84°/0·3 mm. (63·5 g.), was refractionated and the following arbitrary fractions collected: (*a*) 4·0 g., b. p. 58—65°/0·1 mm., $n_D^{19°}$ 1·4862 (Found: Br, 35·5%); (*b*) 47·7 g., b. p. 62—77°/0·1 mm., $n_D^{19°}$ 1·4737 (Found: Br, 35·6%. Calc. for monobromopropionylpropionic ester, $C_8H_{13}O_3Br$; Br, 33·7%).

Ethyl β-Propionylacrylate.—The bromo-ester (fraction *b*; 31·5 g., fraction *a* may also be used) was mixed with dry pyridine (41 c.c.), the heat which was developed after a short time being moderated by occasional cooling. When the heat of reaction began to abate, the deep red mixture was heated on the steam-bath under reflux for 2 hours. After cooling it was poured into 2N-hydrochloric acid (200 c.c.) and extracted with ether. The ethereal extract was washed twice with water, dried (Na_2SO_4), and evaporated on the steam-bath. The residue was distilled under reduced pressure, the product (2·77 g.) being a straw coloured liquid, b. p. 92—94°/9 mm., $n_D^{18°}$ 1·4515. An approximately equal amount of tarry non-volatile residue remained. The 2 : 4-dinitrophenylhydrazone, yellow sheaves (from ethanol), had m. p. 135° alone or mixed with the 2 : 4-dinitrophenylhydrazone of the ester otherwise obtained as described below. On hydrolysis with 2N-hydrochloric acid the liquid yielded propionylacrylic acid (30—40%), identified by m. p. and mixed m. p. with the crystalline acid obtained as described below.

α-Bromo-β-carbethoxypropionyl Chloride.—(Cf. Volhard, *Annalen*, 1887, **242**, 156.) Bromosuccinic acid (40 g.) and thionyl chloride (75 g.) were refluxed for 3 hours on the steam-bath. Excess of thionyl chloride was removed under reduced pressure, and ethyl alcohol (10 g.) was added to the residue in small portions at a time, with shaking. Finally the mixture was warmed on the steam-bath for 10 minutes, cooled, and treated with an equal volume of water. The resulting oil was washed 3 or 4 times with water to remove di-acid, dissolved in ice-cold sodium carbonate solution, and washed with ether to remove di-ester. The aqueous layer, after acidification with 2N-hydrochloric acid, was extracted with ether, and the ethereal solution was washed with water, treated with charcoal, filtered, and dried ($CaCl_2$). After removing the ether under reduced pressure, ethyl hydrogen bromosuccinate was obtained as a heavy brown oil (yield 32 g.) (Equiv. by titration, 230. Calc. for $C_6H_9O_4Br$: equiv., 225). It decomposed on attempted distillation under reduced pressure. It was converted to the acid chloride by refluxing for 2 hours with thionyl chloride (16 c.c.) followed by removal of excess of thionyl chloride under reduced pressure.

Condensation with ethylzinc iodide. The above acid chloride was dissolved in dry toluene (35 c.c.) and cooled to −20° (internal temperature). A solution of ethylzinc iodide (32 g., calculated on a 75% yield from ethyl iodide) in toluene was run in slowly with frequent shaking and at such a rate that the temperature of −20° was maintained. If the temperature fell below this, little or no reaction took place, while at higher temperatures tarring occurred. When the addition was complete the mixture was kept at −20° for about 5 hours with frequent shaking, by which time the

characteristic odour of acid chloride had disappeared. The temperature was raised to 0°, and ice water (100 c.c.) run in. The toluene solution was washed with 20% sulphuric acid, concentrated ammonium sulphate solution, water, saturated potassium bicarbonate, very dilute sodium thiosulphate solution, and finally with water. It was then dried (Na_2SO_4), and the toluene was removed under reduced pressure. There was thus obtained a heavy brown oil (*ca.* 18 g.). On attempted distillation at <1 mm. a few drops of distillate came over at about 80°; the temperature then rose steadily to above 100° and hydrogen bromide was given off. The small amount of distillate rapidly became dark brown and, on treatment with 2 : 4-dinitrophenylhydrazine, yielded the same crystalline derivative, m. p. 135°, as was obtained above from ethyl β-propionylacrylate.

Removal of hydrogen bromide. The crude reaction product (12·5 g.) was dissolved in a mixture of quinoline (12·5 g.) and alcohol (16 c.c.) and heated gently on the steam-bath for 90 minutes. After cooling, water (20 c.c.) was added and the oily layer separated by means of ether, washed with a small quantity of dilute hydrochloric acid and water, and dried ($CaCl_2$). After removing the solvent, the residue was distilled under reduced pressure and a fraction (4—5 c.c.), b. p. 97—100°/10 mm., was collected. The latter was redistilled, b. p. 109—110°/17 mm., $n_D^{20°}$ 1·4520 (Found : C, 60·5; H, 7·1. $C_8H_{12}O_3$ requires C, 61·5; H, 7·7%). It yielded a crystalline 2 : 4-dinitrophenylhydrazone, m. p. 135°, identical with that obtained from *ethyl β-propionylacrylate* made by the other methods.

While the same 2 : 4-dinitrophenylhydrazone was always obtained in these experiments, and the distillate usually had b. p. and refractive index similar to those given above, the figures for C and H were always considerably lower than those required for pure ethyl propionylacrylate. Hydrolysis of a sample with particularly low figures (Found : C, 56·3; H, 7·1%), with 2N-hydrochloric acid yielded mainly fumaric acid, and only a small amount of propionylacrylic acid which was identified as its 2 : 4-dinitrophenylhydrazone, m. p. 210—216° (see below).

Ethyl Propionyl-fumarate (-maleate).—A mixture of ethyl hydroxyethoxyacetate (34·5 g.) (Traube, *Ber.*, 1907, **40**, 4944), ethyl propionylacetate (35 g.) (Willstätter and Clarke, *Ber.*, 1914, **47**, 298), and acetic anhydride (48 g.) was heated under reflux on the steam-bath for 9 hours. After cooling, the mixture was diluted with ether (100 c.c.) and shaken with water (80 c.c.) to which ammonia (*d* 0·88) was added in small portions until the aqueous layer was faintly alkaline. The ethereal layer was finally washed with water and dried (Na_2SO_4). After removal of the ether the residue was fractionated in a vacuum. The *product* (31 g.) had b. p. 122—124°/1 mm., $n_D^{20°}$ 1·4568 (Found : C, 57·2; H, 6·95. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in yellow needles, m. p. 162—163° (Found : N, 13·7. $C_{17}H_{20}O_8N_4$ requires N, 13·7%).

β-Propionylacrylic Acid.—Ethyl propionylfumarate (41 g.) and 2N-hydrochloric acid (410 c.c.) were boiled under reflux for 3½ hours. The yellow solution was cooled, saturated with ammonium sulphate, and extracted several times with ether. After being washed with saturated ammonium sulphate solution, the ethereal solution was evaporated and the residue dried in a vacuum. It was dissolved in warm benzene (20 c.c.) and on cooling propionylacrylic acid (3·7 g.) crystallised in long narrow sheaves. On recrystallisation from benzene the *acid* had m. p. 107—108° (Found : C, 56·0; H, 6·4. $C_6H_8O_3$ requires C, 56·25; H, 6·25%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol had m. p. 210—216° (Found : N, 18·15. $C_{12}H_{12}O_6N_4$ requires N, 18·2%).

Hydrolysis of ethyl propionylfumarate with boiling 20% hydrochloric acid yielded propionylacrylic acid and a small amount of a crystalline *acid*, minute rhombs (from water), m. p. 258—260° (decomp.) (Found : C, 60·7; H, 5·9. $C_{12}H_{14}O_5$ requires C, 60·6; H, 5·9%). The substance was obtained in too small amount for further examination.

Conversion into the ester. Finely divided calcium carbonate (2·5 g.) was added gradually to a warm solution of propionylacrylic acid (5·7 g.) in water (24 c.c.). The mixture was warmed on the steam-bath for a further 30 minutes and filtered hot, and the residue washed with warm water (10 c.c.). The cold filtrate was treated with a solution of silver nitrate (8·0 g.) in water (10 c.c.), and cooled in ice; the silver salt was then filtered off, washed with small quantities of ice water, and dried in a vacuum with protection from light (yield 9·3 g.). The finely powdered salt was heated under reflux on the steam-bath with a solution of ethyl iodide (7·73 g.) in dry chloroform (40 c.c.) for 2 hours. After cooling, the silver iodide was filtered off and washed several times with chloroform. The combined chloroform solutions were washed with sodium bicarbonate solution, then with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the *ester* then distilled as a pale straw coloured liquid (yield 4·0 g.), b. p. 103—104°/12 mm., 94—96°/8 mm., $n_D^{20°}$ 1·4532 (Found : C, 61·7; H, 7·7. $C_8H_{12}O_3$ requires C, 61·6; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in long yellow sheaves, m. p. 135° (Found : N, 16·8. $C_{14}H_{16}O_6N_4$ requires N, 16·7%). The ester on hydrolysis with 2N-hydrochloric acid gave the acid in 40% yield.

Formylation of Ethyl β-Propionylacrylate.—To a stirred suspension of finely powdered sodium methoxide (1·37 g.) in dry ether (20 c.c.), cooled below 0°, a mixture of ethyl propionylacrylate (3·96 g.) and ethyl formate (1·98 g.) was added gradually during 30 minutes. The mixture which had become progressively yellow to dark brown was stirred below 0° for a further hour, then kept at 0° for 20 hours. The brick-red sodium salt was filtered, washed with dry ether, and dried in a vacuum (yield 4·6 g.). It was added in portions to a stirred mixture of 0·9N-acetic acid (25 c.c.) and ether (70 c.c.) cooled below 0°. The ethereal layer was washed several times with water, evaporated, and the residue dried in a vacuum. The product (1·8 g.) was a yellow brittle gum, m. p. 54—61° (Found : C, 59·9; H, 6·3. Calc. for $C_9H_{12}O_4$ (II) : C, 58·7; H, 6·5. Calc. for the β-diketone, $C_{14}H_{18}O_5$, which might arise from the condensation of two molecules of ethyl β-propionylacrylate : C, 63·2; H, 6·8%). The substance could not be rendered crystalline by treatment with solvents or by absorption on a column of alumina from benzene solution. It decomposed on attempted distillation (0·1 mm.). In alcoholic solution it gave a marked red colouration with ferric chloride solution. With saturated cupric acetate solution, an ethereal solution gave an olive-green copper salt which, after partial purification by fractional precipitation, crystallised (unsatisfactorily) from 70% ethanol, and had m. p. 210—215° (decomp.) (Found : C, 48·0; H, 5·3; Cu, 14·8. Calc. for $C_{18}H_{22}O_8Cu$: C, 50·3; H, 5·1; Cu, 14·7. Calc. for Cu salt of the possible β-diketone, $C_{28}H_{34}O_{10}Cu$: C, 56·7; H, 5·7; Cu, 10·6%). There was no improvement in C and H figures for the substance regenerated from this copper salt.

Formylation of Ethyl Propionylfumarate.—Attempted formylation with sodium methoxide as condensing agent resulted in a recovery of *ca.* 80% of starting material after 48 hours' action at 0°.

To a stirred suspension of powdered sodium (1·04 g.) in dry toluene (20 c.c.) cooled at 0° was added gradually a mixture of ethyl propionylfumarate (10·2 g.) and ethyl formate (3·5 g.); stirring at 0° was continued for 5 hours, and the mixture allowed to stand at 0° for a further 40 hours. The sodium salt was precipitated by stirring with light petroleum (b. p. 60—80°) (50 c.c.), filtered, washed with light petroleum, and dried in a vacuum (yield 9·7 g.). It was added in portions to a stirred mixture of 0·9N-acetic acid (40 c.c.) and ether (60 c.c.) at 0°. The ethereal layer was washed three times with water and dried (Na_2SO_4). After removal of solvent the residual oil was dried at 60°/20 mm. (5·9 g.). From this by solution in ether, addition of light petroleum, and scratching, a substance (0·5 g.) having the composition of (VI) or (VII) was obtained, m. p. 169—170° after recrystallisation from benzene (Found : C, 58·5; H, 6·35; OEt, 33·2. Calc. for $C_{10}H_{16}O_9$: C, 58·5; H, 6·3; OEt, 32·9%). The substance was readily soluble in sodium bicarbonate solution, and in alcoholic solution gave a deep red colouration with ferric chloride. The residual oil was dissolved in ether, extracted with sodium bicarbonate solution, and, after evaporation of solvent, fractionated in high vacuum. The following fractions were collected : (*a*) b. p. 86—90° (bath temperature)/0·05 mm. (1 g.), (*b*) b. p. 164—170° (bath temperature)/0·05

mm. (2·8 g.). Fraction (*b*) was redistilled. It gave a deep red colouration with ferric chloride in alcoholic solution, and was presumed to be *ethyl 6-hydroxy-4-keto-3-carbethoxy-5-methyl-*$\Delta^{2:5}$*-hexadienoate* (Found: C, 56·6; H, 6·8. $C_{12}H_{16}O_6$ requires C, 56·3; H, 6·3%). There were indications of crystallisation on standing in absence of air. Fraction (*a*) on redistillation had b. p. 105°/0·3 mm. (Found: C, 55·6; H, 7·5; OEt, 47·6. Calc. for $C_3H_7O_4(OEt)_3$: C, 55·6; H, 7·3; OEt, 44·7%). The substance, which has not been identified, gave no colouration with ferric chloride. With 2 : 4-dinitrophenylhydrazine it gave a derivative, crystallising from ethanol in yellow needles, m. p. 155° (Found: N, 14·3%).

The work described in this paper was carried out as part of a programme of the Therapeutic Research Corporation of Great Britain Limited to the Directors of which acknowledgments are made. We have to thank Mr. S. Bance, B.Sc., for the various semi-microanalyses.

RESEARCH LABORATORIES, MAY & BAKER LTD., DAGENHAM. [*Received, December 1st*, 1945.]

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86. *The Oxidation of Diphenylamine and of its* N-*Derivatives. Part I. Oxidation of* >N·CH$_2$R *to* >N·CO·R.

By JAMES FORREST, DAVID A. LIDDELL, and S. HORWOOD TUCKER.

N-Alkyl- and *N*-aralkyl-diphenylamines have been prepared, and their oxidation by potassium permanganate in acetone or pyridine studied. *N*-Ethyldiphenylamine and certain of its nitro- and bromo-derivatives give *N*-acetdiphenylamides, and *N*-benzyldiphenylamine gives *N*-benzdiphenylamide; all other *N*-substituted diphenylamines investigated either do not react or give tetraphenylhydrazine.

N-Benzylcarbazole can be similarly oxidised to *N*-benzoylcarbazole.

A method of preparing dipicrylamine from *N*-acetdiphenylamide is described.

WHEREAS the oxidation of diphenylamine by potassium permanganate in acetone gives rise to tetraphenylhydrazine, oxidation by sodium dichromate in acid solution gives *NN'*-diphenylbenzidine (Wieland and Gambarjan, *Ber.*, 1906, **39**, 1501; Wieland, *Ber.*, 1913, **46**, 3300; 1919, **52**, 889; Marqueyrol and Muraour, *Bull. Soc. chim.*, 1914, **15**, 186; Sarver and Johnson, *J. Amer. Chem. Soc.*, 1935, **57**, 329. Cf. Kadeira, *Ber.*, 1905, **38**, 3575). Similarly, oxidation of *N*-methyldiphenylamine in acid solution gives rise to *NN'*-diphenyldimethylbenzidine (Wieland, *Ber.*, 1919, **52**, 889; Maitland and Tucker, *J.*, 1927, 1388). On the other hand, oxidation under acid conditions failed to convert *N*-ethyldiphenylamine into a benzidine derivative. Since, however, oxidation of *N*-methyldiphenylamine by potassium permanganate in acetone had given *NN'*-diphenyldimethylbenzidine (Maitland and Tucker, *loc. cit.*), the same oxidising agent was tried on *N*-ethyldiphenylamine, with the quite unexpected result that *N*-acetdiphenylamide was isolated (15%). Modification of the method using pyridine instead of acetone raised the yield (30%).

2-Nitro-, 2 : 4-dinitro-, and 4 : 4'-dibromo-*N*-ethyldiphenylamine also, by oxidation, gave the corresponding *N*-acetyl derivatives, but in small yields: on the other hand *N*-benzyldiphenylamine gave *N*-benzdiphenylamide in excellent yield (70%). The method failed to give the corresponding >N·CO– (or >N·C(OH)<) derivative when tried with *N*-propyl-, *N-iso*propyl-, *N*-butyl-, *N-iso*butyl-, *N*-amyl-, *N*-β-phenylethyl-, 4 : 4'-dibromo-*N*-propyl-, and 2 : 4 : 2' : 4'-tetrabromo-*N*-ethyl-diphenylamine. The last three were recovered unchanged, but the others gave small yields of tetraphenylhydrazine.

Acyldiphenylamines may arise *via* carbinolamines, >N·CH(OH)R, the fission and subsequent oxidation of which would explain the formation of tetraphenylhydrazine; *N*-acyldiphenylamines were found to be stable under the conditions employed. Attempts to verify the above suggestion were, however, fruitless; although the reductive condensation of diphenylamine with aldehydes indicates the transitory existence of the carbinolamines (Skita, Keil, and Havemann, *Ber.*, 1933, **66**, 1400) they could not be prepared by interaction of diphenylaminemagnesium bromide and appropriate aldehydes.

N-Alkyl- and -aralkyl-diphenylamines have been prepared by acting upon diphenylamine with (*a*) alcohols and hydrochloric acid (Girard, *Bull. Soc. chim.*, 1875, **23**, 2); (*b*) alkyl sulphates with or without addition of alkali (Ullmann, *Annalen*, 1903, **327**, 104; Wieland, *Ber.*, 1919, **52**, 890; Gibson and Vining, *J.*, 1923, **123**, 831); (*c*) alkyl iodides (Bardz, *Z. angew. Chem.*, 1871, 469) and bromides; (*d*) aldehydes and ketones with hydrogen and a catalyst (Skita, Keil, and Havemann, *loc. cit.*). By modifications of these methods we have prepared the compounds shown in the table in the yields there recorded.

Yields (%) *of* N-*substituted-diphenylamines.*

N-Substituted-diphenylamine.	Me.	Et.	Pr$^\alpha$.	Pr$^\beta$.	Bu$^\alpha$.	Bu$^\beta$.	*n*-Amyl.	Ph·CH$_2$.	Ph·[CH$_2$]$_2$.
By alkyl sulphates	80	65—75	40	—	—	—	—	—	—
By alkyl iodides	40	80	50	50	40	33	30	—	—
By alkyl or aralkyl bromides ...	—	0	2	2	30	—	—	—	45
By aralkyl chloride	—	—	—	—	—	—	—	90—95	—

The alkyl iodides showed most general applicability but the yields steadily decreased with increase of molecular weight of the alkyl group. Chain branching seemed to have little effect—in strong contrast to the effect in the method of Skita, Keil, and Havemann where yields were greatly depressed when a branching methyl radical was attached in the α-position.

Alkylation of diphenylaminemagnesium bromide was successful in the preparation of *N*-ethyldiphenylamine, but unsuccessful for higher members.

N-Ethylcarbazole was unattacked by permanganate in boiling acetone or pyridine, but *N*-benzylcarbazole gave a small amount of *N*-benzoylcarbazole.

Nitration of *N*-acetdiphenylamide with a mixture of concentrated nitric and sulphuric acids gave 2 : 4 : 2′ : 4′-tetranitrodiphenylamine, the intermediate acetyl derivative being very susceptible to hydrolysis. Solution of this tetranitro-derivative in fuming nitric acid followed by addition of sulphuric acid precipitated 2 : 4 : 6 : 2′ : 4′ : 6′-hexanitrodiphenylamine (dipicrylamine) in almost theoretical yield.

Experimental.

In preparation of the tertiary amines later described, separation from unchanged diphenylamine was effected by one or a combination of the following three methods : the reaction mixture was (1) oxidised by potassium permanganate in acetone—diphenylamine being thus converted into tetraphenylhydrazine—and the tertiary amine obtained by distillation; (2) treated with excess of concentrated hydrochloric acid which precipitated diphenylamine hydrochloride leaving the tertiary amine in solution; (3) treated with acetyl chloride in presence of sodium acetate, and the *N*-acetdiphenylamide separated in crystalline form by adding light petroleum (b. p. 60—80°) and cooling to 0°. Acetic anhydride was less effective, even at the b. p.

For the lowest members method (2) was adopted followed by (3), except that, when *N*-ethyldiphenylamine was being prepared for subsequent oxidation, method (3) was replaced by (1). Method (2) was limited to the *N*-methyl-, *N*-ethyl-, and *N*-propyl-diphenylamines since the higher alkyldiphenylamines are practically insoluble in concentrated hydrochloric acid; these latter were separated by method (3). (Cf. I.G. Farbenindustrie, B.P. 333,349.)

Preparation of N-*Ethyldiphenylamine.*—(A) *Using ethyl sulphate* (Gibson and Vining, *loc. cit.*). Diphenylamine (42·3 g.; 1 mol.), ethyl sulphate (57·7 g. = 49 c.c.; 1·5 mol.), and anhydrous potassium carbonate (51 g.; 1·5 mol.) were mixed and heated in a flask, fitted with a short fractionating column, in an air-bath kept at 175—180° for 2 hours. The mixture was occasionally shaken. A small amount of ethanol, ether, and water distilled. The residue was treated with dilute hydrochloric acid, rendered alkaline, extracted with light petroleum (b. p. 60—80°), and fractionally distilled. The fraction b. p. 150—170°/15 mm. was treated with equal weights of anhydrous sodium acetate and acetyl chloride, the latter being added in four portions with vigorous shaking. The mixture was poured into water, boiled, and extracted whilst warm with light petroleum (b. p. 60—80°). The dried solution was kept for several hours at 0°, filtered from *N*-acetdiphenylamide, and the filtrate fractionally distilled yielding *N*-ethyldiphenylamine, b. p. 152—153°/12 mm. (35 g.; yield, 70%). The yield was slightly reduced when heating was at 165—170°.

(B) *By the Grignard reaction* (cf. Cope, *J. Amer. Chem. Soc.* 1934, **56**, 1578; King, King, and Muir, this vol., p. 5). Diphenylaminemagnesium bromide (1 mol.) was prepared from diphenylamine and ethylmagnesium bromide in ether with exclusion of air. A solution of ethyl sulphate (2 mols.) in ether was added, and *N*-ethyldiphenylamine isolated in the usual way (yield, 80%). Propyl iodide, propyl sulphate, propyl *p*-toluenesulphonate, butyl iodide, and butyl *p*-toluenesulphonate did not react with diphenylaminemagnesium bromide (or iodide) in ether or in boiling toluene or xylene.

(C) *From alkyl iodides.* A mixture of diphenylamine (1 mol.), ethyl iodide (1·5 mols.), and anhydrous potassium carbonate (1·5 mols.) was boiled for 48 hours and *N*-ethyldiphenylamine isolated (yield, 80%). The experiment failed when ethyl bromide replaced the iodide.

Other *N*-alkyldiphenylamines were similarly prepared, using alkyl iodides, in yields given in the table (p. 454).

N-iso*Propyldiphenylamine*, prepared from *iso*propyl iodide, had b. p. 160—165°/15 mm. (22 g.; yield, 52%) (Found : C, 85·2; H, 7·8. $C_{15}H_{17}N$ requires C, 85·3; H, 8·1%).

4 : 4′-*Dibromo*-N-iso*propyldiphenylamine.*—*N-iso*Propyldiphenylamine (5 g.) in glacial acetic acid (40 c.c.) was stirred whilst a solution of bromine (7·7 g.) in glacial acetic acid (20 c.c.) was slowly added. When evolution of hydrogen bromide had ceased, the white crystalline *product*, recrystallised from ethanol, had m. p. 92° (8·5 g., yield 96%) (Found : C, 48·7; H, 4·3; N, 3·9. $C_{15}H_{15}NBr_2$ requires C, 48·8; H, 4·1; N, 3·8%).

The dibromo-derivatives of *N*-ethyl-, *N*-propyl-, and *N*-butyl-diphenylamines were similarly prepared (Skita, Keil, and Havemann, *loc. cit.*).

N-n-*Amyldiphenylamine* was prepared as described for the preparation of *N-iso*propyldiphenylamine, and also by heating diphenylamine (33·8 g.; 1 mol.), *n*-amyl alcohol (17·6 g.; 1 mol.), and zinc chloride (40 g.; 1·5 mols.) at 120° for 4 hours. After acetylation of the reaction product, and removal of the crystalline *N*-acetdiphenylamide, the residual oil was fractionated and gave *N*-*n*-amyldiphenylamine, b. p. 190—195°/12 mm. (10·5 g.; yield, 21%) (Found : C, 85·3; H, 8·5. $C_{17}H_{21}N$ requires C, 85·35; H, 8·8%). Under these conditions the risk of contamination of the *n*-amyl by isomerised amyl derivatives is slight (Whitmore, Karnatz, and Popkin, *J. Amer. Chem. Soc.*, 1938, **60**, 2540).

N-β-*Phenylethyldiphenylamine.* Diphenylamine (16·9 g.; 1 mol.), β-phenylethyl bromide (37 g.; 2 mols.), and anhydrous potassium carbonate (20 g.; 1·5 mols.) were heated at 130° for 5 hours. After addition of water the separated oil was distilled in a vacuum; β-phenylethyl bromide (b. p. 100°/10 mm.), diphenylamine (b. p. 150—160°/10 mm.) and *N*-β-phenylethyldiphenylamine (b. p. 220—230°/10 mm.) were obtained. The last crystallised from light petroleum (b. p. 40—60°) in large octahedra; it was recrystallised from methanol; the *compound* then had m. p. 61—63° (15 g.; yield 55%) (Found : C, 87·9; H, 6·8; N, 5·1. $C_{20}H_{19}N$ requires C, 87·9; H, 7·0; N, 5·1%). β-Phenylethyl chloride similarly (at 150° for 4 hours) gave the same product (50% yield); but β-phenylethyl iodide (refluxing for 10 hours) gave unchanged diphenylamine and β-phenylethyl iodide, with β-phenylethanol and styrene.

N-*Benzyldiphenylamine.* Diphenylamine (34 g.; 1 mol.), benzyl chloride (30 g.; 1·2 mols.), and anhydrous potassium carbonate (35 g.; 1·2 mols.) were heated at 200° for 2 hours. The melt was steam distilled to remove unchanged benzyl chloride, the residue extracted with light petroleum (b. p. 60—80°), and the isolated *N*-benzyldiphenylamine crystallised from ethanol; it had m. p. 86° (44 g.; yield, 88%).

Oxidation of N-*Ethyldiphenylamine.*—Acetone was purified by Werner's method (*Analyst*, 1933, **58**, 335). Usually it was further boiled for ½ hour with excess of potassium permanganate, distilled, dried, and redistilled.

N-Ethyldiphenylamine (2 g. purified by method (2) followed by (1), above) was dissolved in this pure acetone (20 c.c.) and very finely powdered potassium permanganate (5 g.) added in small portions : the mixture was boiled on the water-bath after each addition. After having been boiled for 45 minutes the whole was treated with sulphurous acid to dissolve manganese oxides, and the precipitated oil extracted from the warm solution with light petroleum (b. p. 60—80°). The evaporated extract gave a mixture of crystals and oil; the separated crystals recrystallised from light petroleum as *N*-acetdiphenylamide, m. p. 100° (0·32 g.; yield 15%). The m. p. was not depressed when mixed with an authentic specimen prepared from diphenylamine and boiling acetic anhydride. The separated oil contained unchanged *N*-ethyldiphenylamine.

Addition of sodium bicarbonate, magnesium sulphate, or anhydrous sodium sulphate to the reaction mixture appeared to have no effect; but addition of anhydrous sodium carbonate seemed to give slightly cleaner products. Potassium hydroxide was disadvantageous.

Later it was found that the yield of *N*-acetdiphenylamide was doubled when pyridine replaced the acetone. Calcium permanganate could not be used with pyridine since the two reacted, producing incandescence within the liquid. The above method was used in the oxidation of other *N*-substituted diphenylamines, except that sodium bicarbonate (equal in weight to that of the permanganate used) was added. It was probably an unnecessary addition.

N-Benzyldiphenylamine, oxidised in acetone by potassium permanganate in presence of sodium bicarbonate, gave *N*-benzdiphenylamide, m. p. 177° (yield, 70%).

4 : 4′-Dibromo-*N*-ethyldiphenylamine similarly oxidised gave 4 : 4′-*dibromo*-N-*acetdiphenylamide*, m. p. 180° (yield, 8%). (Found: N, 3·8. $C_{14}H_{11}ONBr_2$ requires N, 3·8%).

2-Nitro-*N*-ethyldiphenylamine gave a mixture from which yellow crystals, m. p. 134—135°, of 2-nitro-*N*-acetdiphenylamide (Kehrmann and Baumgartner, *Helv. Chim. Acta*, 1926, **9**, 673) were separated in very small yield by hand-picking. The corresponding 2 : 4-dinitro-compound gave similarly, by crystallisation from methanol, 2 : 4-dinitro-*N*-acetdiphenylamide, m. p. 154°.

With the other *N*-alkyldiphenylamines oxidation in acetone yielded tetraphenylhydrazine (yield ~15%). This was nearly insoluble in ethanol but crystallised in colourless prisms from ethyl acetate and then from toluene. Owing to the ease with which it turned green it was difficult to raise the m. p. above 144° (Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499; cf. Chattaway and Ingle, *J.*, 1895, **67**, 1091, who give m. p. 147°).

N-*Propiondiphenylamide*.—(*a*) Propionyl chloride and anhydride prepared by the usual methods give poor yields, but the chloride prepared (yield 80%) by means of benzoyl chloride (Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325) gave with diphenylamine in presence of anhydrous sodium acetate an excellent yield of *N*-propiondiphenylamide, m. p. 58° (cf. v. Mayer and Nicolaus, *J. pr. Chem.*, 1861, **82**, 530). (*b*) Diphenylaminemagnesium bromide, prepared in the usual way from ethylmagnesium bromide in ether solution, was treated with ethyl propionate (yield, 52%). (Cf. Hardy, *J.*, 1936, 398.)

Dipicrylamine (2 : 4 : 6 : 2′ : 4′ : 6′-hexanitrodiphenylamine).—*N*-Acetdiphenylamide (12 g.) was added to a mixture of concentrated nitric acid (50 c.c.) and concentrated sulphuric acid (25 c.c.) at 15°. On stirring, the amine dissolved and the solution turned green; as the temperature rose spontaneously to 65° the colour changed through brown and orange to red. The temperature was slowly raised to 70—75°; a crystalline yellow precipitate then formed. The mixture was finally heated on the boiling water-bath for 1 minute. 2 : 4 : 2′ : 4′-Tetranitrodiphenylamine, m. p. 198°, was obtained (~100%). (Cf. Kehrmann and Baumgartner, *loc. cit.*, on ease of hydrolysis of the acetyl derivative.) The tetranitrodiphenylamine was dissolved in the minimum quantity of fuming nitric acid (*d* 1·5); addition of concentrated sulphuric acid to this solution precipitated dipicrylamine (exothermic reaction), m. p. 238° (yield, 95%).

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87. *Amorphous Carbon.*

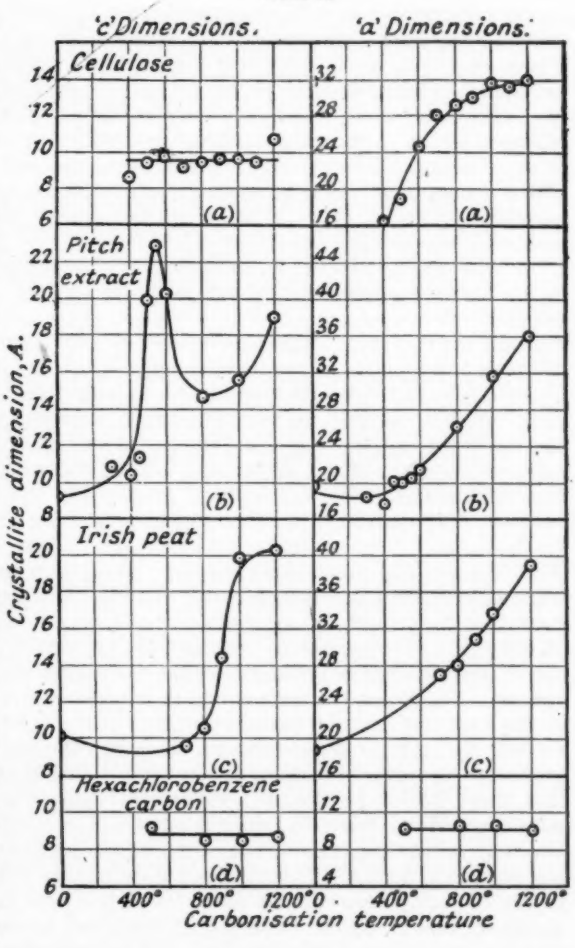
By J. GIBSON, M. HOLOHAN, and H. L. RILEY.

X-Ray diffraction photographs of the so-called "amorphous" carbons have hitherto been interpreted as indicating that they consist of exceedingly minute turbostratic graphite crystallites: this view requires modification in the case of cokes and chars prepared at temperatures below 1200°. The nature of the organic substance, from which such carbons are prepared, is an important factor in determining their crystallographic character. It has been found possible to prepare carbons which are completely amorphous, *i.e.*, that give no coherent diffraction of *X*-rays, and indications have been obtained of three-dimensional, covalent cross-linking in such carbons. The bearing of these results on the crystallographic character of cokes and chars is discussed.

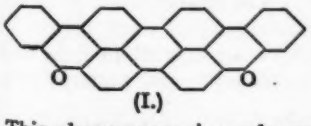
THE term "amorphous carbon" is usually employed to describe more or less impure forms of carbon which are devoid of any obvious crystalline characteristics. Debye and Scherrer (*Physikal. Z.*, 1917, **18**, 291) found that such carbons, prepared by a variety of methods, all gave essentially the same type of *X*-ray powder photograph with the maxima of the diffuse diffractions in the same positions: "Amorphe Kohle ist also Graphit in einer so feinen Verteilung, wie dieselbe durch mechanische Mittel niemals erreicht werden kann". From the diffraction broadening they estimated that the individual "molecule" often contains only about 30 atoms. Detailed *X*-ray examination of a large number of related series of "amorphous" carbons (see Blayden, Gibson, and Riley, "The Ultra-Fine Structure of Coals and Cokes," B.C.U.R.A., London, 1944, 176—231: *J. Inst. Fuel*, 1945, War Time Bulletin, 117) indicates that the above view requires modification, and further work has shown that truly amorphous carbon does exist. By measuring the half-peak widths of the diffraction bands in *X*-ray powder photographs it is possible to follow the growth of the carbon crystallites with increasing temperature of carbonisation. The inner (002) diffraction halo gives the average height (*c* dimension) of the minute carbon crystallites, conceived as small cylinders, and the less intense (10) halo gives the average diameter (*a* dimension). The corrected half-peak width (β) of the 002 diffraction is related to the *c* dimension (L) by Jones's formula $\beta = 1{\cdot}0\lambda/L\cos\theta$, where λ is the *X*-ray wave-length, and θ the Bragg angle: the half-peak width of the 10 diffraction, which is a cross-lattice diffraction, is related to the *a* dimension by Warren's formula, $\beta = 1{\cdot}84\lambda/L\cos\theta$ (*Physical Rev.*, 1942, **49**, 693). Fig. 1 summarises the results of these crystallite growth studies already obtained. Fig. 1*a* shows the average *c* and *a* dimensions of the crystallites present in chars obtained by carbonising pure cellulose at 5° per min. up to various temperatures. The increase in the *a* dimension (*i.e.*, experimentally, the sharpening of the 10 diffraction band) is probably due to the progressive lamellar growth of the hexagon layer-planes of carbon atoms, brought about by a process of aromatic condensation which commences at about 200°. The constancy of the *c* dimension is, however, somewhat surprising and suggests that the layer-planes of the individual crystallites are rigidly cross-linked in some way or other. It should be remembered that these chars do not consist of pure carbon but contain appreciable quantities of

oxygen and hydrogen, and that it is only when the carbonisation temperature has been well above 1000° that the product obtained approximates to pure carbon. There is evidence that it is these foreign oxygen and possibly also nitrogen and sulphur atoms which play a crucial rôle in the structure of these rigid turbostratic crystallites. The word "turbostratic" was coined by Biscoe and Warren (*J. Appl. Physics*, 1942, **13**, 364) to describe those mesomorphous crystallites in which the layer-planes are stacked parallel to each other and equally spaced along the *c* axis, but are otherwise disordered along the *a* and *b* axes: such crystallites show only 00*l* and *hk* diffractions. There is much evidence in support of this hypothesis of the crucial rôle of oxygen atoms in carbon crystallites, *e.g.*, the carbohydrates cellulose, starch, sucrose (see also Hofmann and Sinkel, *Z. anorg. Chem.*, 1940, **245**, 85), and glucose; lignin and wood, *i.e.*, compounds containing a relatively high proportion of oxygen, all give chars on carbonisation which contain crystallites with an average *c* dimension between 9 and 10 A. The carbonising conditions can be varied between wide limits, with respect to both temperature (up to 1200°) and speed, without any consequential change in the half-peak width of the 002 diffraction of the resulting char. If, however, glycine is used as the parent organic substance, or if cellulose is carbonised in an atmosphere of ammonia (Blayden, Gibson, Riley, and Taylor, *Fuel*, 1940, **19**, 24) a similar phenomenon is observed but the constant *c* dimension is now between 12 and 13 A., instead of 9—10 A. The essential chemical difference between the carbohydrate chars and those from nitrogenous organic compounds is that whereas the former contain residual oxygen, in the latter, it is more or less completely replaced by nitrogen (Hook, *Carnegie Schol. Mem. Iron and Steel Inst.*, 1936, **25**, 81), which suggests that these foreign atoms have similar functions in the carbon lattice and that the nitrogen atom is preferentially retained.

FIG. 1.



Perhaps the most convincing evidence in support of this hypothesis is that, if the proportion of oxygen in the parent organic compound falls below a certain value (probably critical), then an entirely different type of *c* dimension curve results. Fig. 1*b* shows the *c* dimension curve obtained on carbonising that part of a bituminous coal pitch which is soluble in carbon tetrachloride. This type of curve is also given by pitches, certain bitumens, bituminous coals, the γ-solvent extracts of coals and certain pure organic compounds. It appears to be characteristic of the presence in the parent carbonaceous substance, of large, stable, lamellar aromatic molecules which contain a small proportion of oxygen: it has been interpreted as follows. The ascending part of the curve, between room temperature and about 500°, suggests the occurrence of a unidimensional crystallisation, brought about by the packing together of stable lamellar molecules. The maximum at about 500° reflects the conversion of a system which consists essentially of independent stable organic molecules, held together by weak dispersion forces (molecular lattice), into one which consists of rigid (cross-linked) carbon crystallites. This fundamental change in the crystallographic character of the system occurs over a relatively narrow range of temperature, the magnitude of which appears to be a function of the proportion of oxygen in the carbonaceous material. If the proportion is large then, as in the case of cellulose, the rigid cross-linked crystallites are formed at a temperature as low as 200°: at the other extreme, certain coal bitumens give *c*-dimension curves showing maxima in the neighbourhood of 550°. If the proportion of oxygen present in the carbonaceous substance is less than the critical proportion, then even with large, relatively complex, highly condensed molecules, the carbon yield obtained on carbonisation is less and there is an increasing tendency for the substance to volatilise. Support for the above interpretation of the variation of the half-peak width has been obtained by a study of the carbonisation of pure organic compounds; *e.g.*, if dibenzanthrone (I) is precipitated quickly, in the cold, from a soluble vat, the product gives a diffuse diffraction pattern (See Plate I*a*). Annealing the compound at temperatures up to 475° brings about a progressive sharpening of the diffractions and the appearance of new diffractions. This phenomenon is analogous to the sharpening of the 002 diffraction with increasing temperature, in the



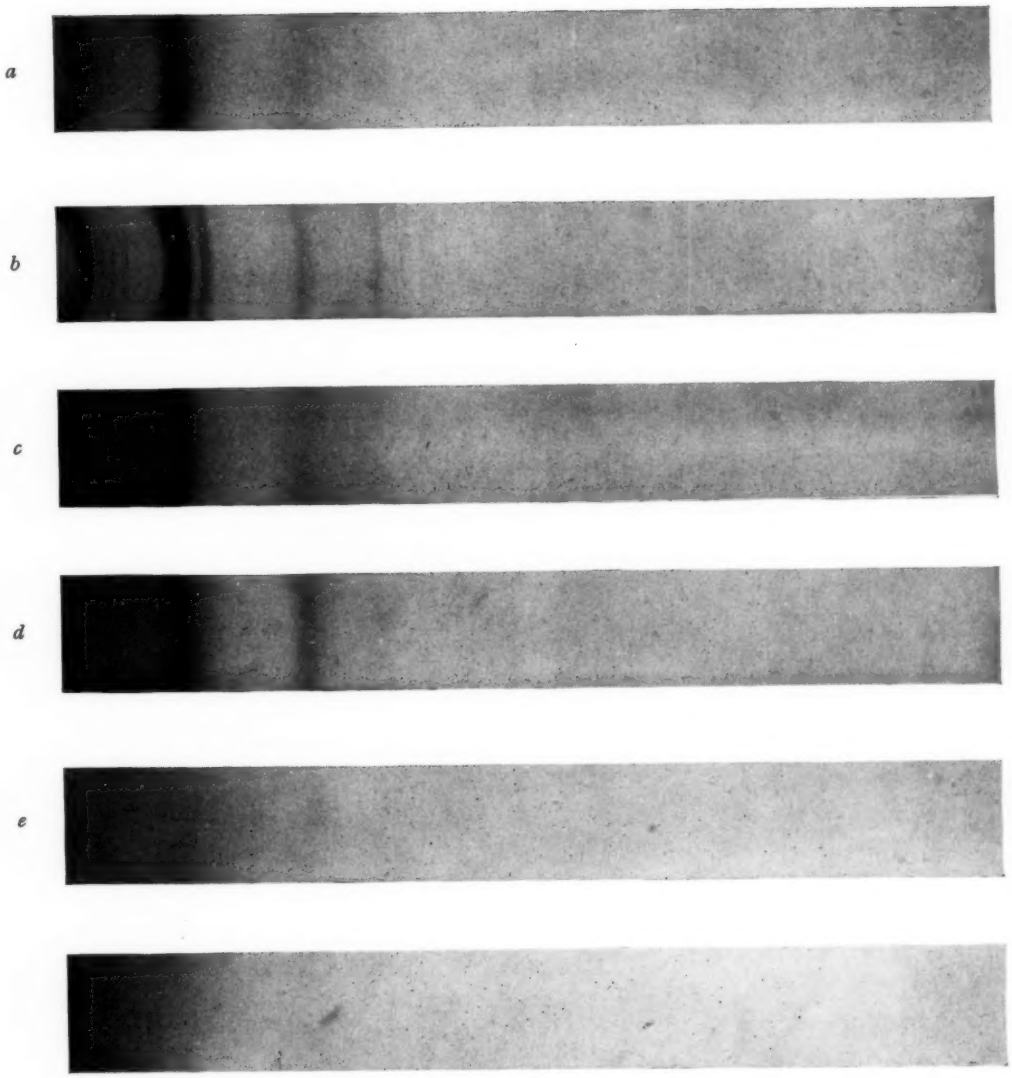
(I.)

case of the pitches and bitumens which are, of course, mixtures of complex molecules of a similar type and consequently do not give line patterns. Between 475° and 500° the diffraction pattern of dibenzanthrone changes completely to that of " amorphous " carbon (see Plate I*b* and *c*).

The interpretation of the descending portion of the *c*-dimension curve between 550° and 900° (Fig. 1*b*) is not quite so clear. The following experimental facts are, however, significant. The phenomenon, as far as our experiments have gone, is of general occurrence. Whenever a carbonaceous substance on heating to some temperature below 550°, gives a product which contains crystallites having an average *c* dimension greater than about 12 A., then a further increase of temperature causes a decrease in the *c* dimension (experimentally, a broadening of the 002 diffraction). Carbonaceous substances with as different histories as South Wales anthracites, chars prepared at 500° from dibenzanthrone and similar compounds, carbonised bitumens, and pitches all show this phenomenon. In the case of bitumens and pitches it is possible partly to prevent the initial increase in the *c* dimension by preliminary oxidation, or extreme dispersion on an inert inorganic colloid, before carbonisation : if this is done then the subsequent decrease in the *c* dimension is much less pronounced. Those organic compounds which contain a high proportion of oxygen and carbonise at relatively low temperatures presumably do so because the cross-linking of the crystallites occurs at low temperatures; it is this that prevents any appreciable growth of the crystallites along the *c* axis in the temperature range 200—500°. When a smaller proportion of oxygen is present the cross linkages are only formed at higher temperatures and consequently, as aromatisation progresses, *c*-dimension growth becomes possible. Further increase in temperature (*i.e.*, above the maximum in the curve; Fig. 1*b*) is accompanied by the evolution of oxygen, in the form of oxides of carbon, presumably with the reduction in the number of the cross-linkages and a consequent possibility of some disruption in the rigid lamellar arrangement of the lattice. The subsequent increase in *c* dimension which occurs above 900° is perhaps facilitated by the remnants of the ordered structure which the system possessed at 550°. In the case of cellulose and similar chars, crystallite growth along the *c* axis shows little tendency to occur at temperatures below 2000°.

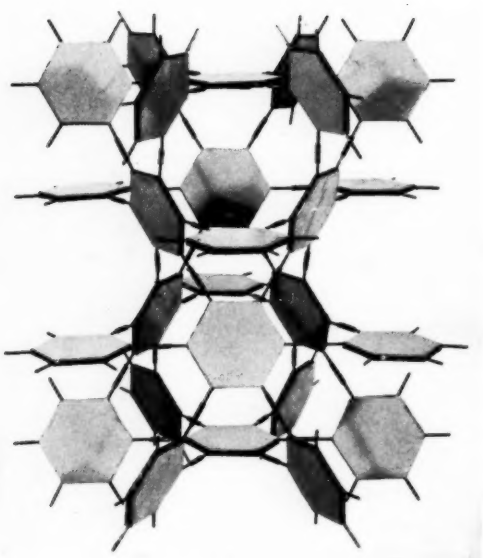
A still further type of *c*-dimension curve is shown in Fig. 1*c* : it is characterised by an abrupt increase in the average *c* dimension of the crystallites in the temperature range 800—1000°. This type of crystallite growth is shown by peats and to a less extent by brown coals and lignites. So far we have only succeeded in reproducing this crystallographic behaviour with laboratory-prepared substances in the case of " bituminised " cellulose and lignin, *i.e.*, cellulose or lignin which has been heated in an autoclave to about 300° with excess of aqueous alkali : these dark products on carbonisation behave crystallographically remarkably similarly to peat. If the peat (but not the bituminised cellulose) is boiled with 2% hydrochloric acid and then carbonised, the chars do not show this pronounced increase in *c* dimension, but, like cellulose chars, have a constant *c* dimension up to 1200°. This result indicates that the anomalous crystallographic behaviour of the peat chars is a consequence of some structural property in the original peat. The pronounced increase in *c* dimension between 800° and 1000° further suggests that the crystallographic nature of low-temperature peat chars is fundamentally different from that of either cellulose chars or bitumen cokes prepared at similar temperatures. Although the 800° peat chars are not pure carbon they contain more than 92% of the element, the balance being largely oxygen and hydrogen : there is little doubt also that they contain some turbostratic crystallites, since the *X*-ray diffraction pattern is not greatly different from that of the corresponding cellulose char. In the case of the peat char, however, the crystallite growth between 800° and 1000° is so great as to suggest the occurrence of some profound atomic rearrangement in this temperature range, perhaps a kind of polymorphic change. Neglecting the finer points in the lattice structure of microcrystalline carbons, such as the variation of the *c* spacing and the parallel stacking of the layer-planes, only two lattice structures of carbon atoms are known, *viz.*, the three-dimensional, covalent diamond lattice and the aromatic, semi-metallic, layer-lattice of graphite; nevertheless, there is a third possible spatial arrangement of carbon atoms. The relationship of this third lattice to that of graphite is shown in Plate II*a*. It can be constructed from the graphite lattice by tilting alternate hexagon rings of the layer-planes and attaching the valencies so freed to those of similarly tilted hexagons in the adjacent planes above and below; Plate II*b* shows the rhombohedral unit cell of such a lattice. The disappearance in this lattice of the flat layer-planes suggests that the resonance energy of such a structure would be much less than that of a corresponding graphite lattice and its existence, therefore, less probable. The lattice contains, however, an orderly network of conjugated double linkages running through the whole structure, and its resonance energy would, therefore, be of an appreciable magnitude. The possible existence of such an arrangement of carbon atoms is suggested by the results of the electron diffraction studies by Karle and Brockway (*J. Amer. Chem. Soc.*, 1944, **66**, 1974), who have established the non-co-planarity of *o*-tetraphenylene. The suggested lattice is a three-dimensional repetition of *o*-tetraphenylene residues (see Plate II *c*). Theilacker and Ewald (*Naturwiss.*, 1943, **31**, 302) have given experimental evidence which they suggest throws doubt on the view that the stability of the triphenylmethyl radical depends upon the co-planar arrangement of the phenyl groups : the chemical similarity of graphite and the triarylmethyls has been pointed out (Riley, *J. Inst. Fuel*, 1937, **10**, 149). Wheland (" The Theory of Resonance," J. Wiley & Sons, New York, 1944, 192 ff.) has discussed the respective parts played by resonance and steric factors in determining the stability of aryl-substituted ethanes and similar compounds. These considerations indicated that an attempt to synthesise a carbon possessing this aromatic cross-linked structure would perhaps give interesting results.

Conditions of interaction which would inhibit the formation of flat, honeycomb net-works of carbon atoms

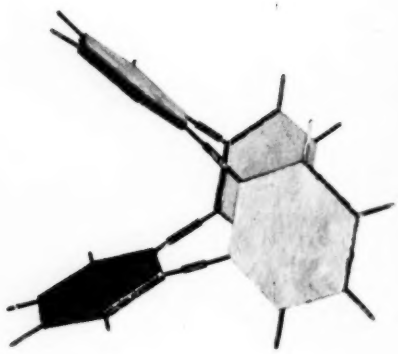


(a) *Dibenzanthrone precipitated cold.*
(b) *Dibenzanthrone heated to* 475°.
(c) *Dibenzanthrone carbonised at* 500°.
(d) *Dibenzanthrone coke heated to* 1000°.
(e) *Hexaiodobenzene char* (1000°).
(f) *Hexachlorobenzene carbon* (1000°).

[*To face p.* 458.



a



c

b

appeared to offer the best possibilities of building up this structure, and the carbonisation of hexaiodobenzene suggested itself as a possible method. Fig. 2 shows a scale drawing of two molecules of hexaiodobenzene, each less one iodine atom: the linking of two such residues with the C_6 rings co-planar is impossible. The C–C bond could only be formed by tilting one ring at a considerable angle with respect to the other. Hexaiodobenzene was accordingly prepared and carbonised in a porcelain boat in a silica tube at 5°/min. up to 1000° in an atmosphere of nitrogen. The carbon residue in the porcelain boat consisted of pseudomorphs of the original crystals of hexaiodobenzene; there was a transluscent carbon mirror on the walls of the silica tube and also a fluffy deposit of carbon. The product was, however, contaminated with silica, probably because of the formation of volatile silicon–iodine compounds, together with the high adsorptive properties of the carbon formed. After extraction of it with hydrofluoric and hydrochloric acids, an *X*-ray powder photograph of the product was made. A reproduction of this is shown in Plate I *e* contrasted with that (*d*) of a carbon prepared by carbonising dibenzanthrone up to 1000°. Small-scale reproductions of microphotometer traces of these two photographs are shown in Fig. 3, *a* and *c*. The powder photographs were made, as far as possible, under identical conditions. The hexaiodobenzene carbon gives practically no coherent scattering of the *X*-rays and indicates that the carbon is almost completely devoid of any ordered structure. If "amorphous" carbon merely consists of extremely minute graphite crystallites, it is difficult to understand how such a disordered structure as hexaiodobenzene-carbon could exist, for the shape of the lamellar hexagon layer-planes alone would cause them to pack together with a fairly high degree of order. A cross-linked structure similar to that shown in Plate II, but highly disordered because of the presence of foreign oxygen and hydrogen atoms, appears to offer a more reasonable explanation of the existence of such a form of carbon (cf. Zachariasen, *J. Amer. Chem. Soc.*, 1932, **54**, 3841, on the structure of silica glasses).

FIG. 2.

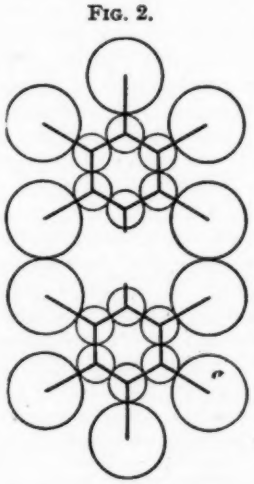
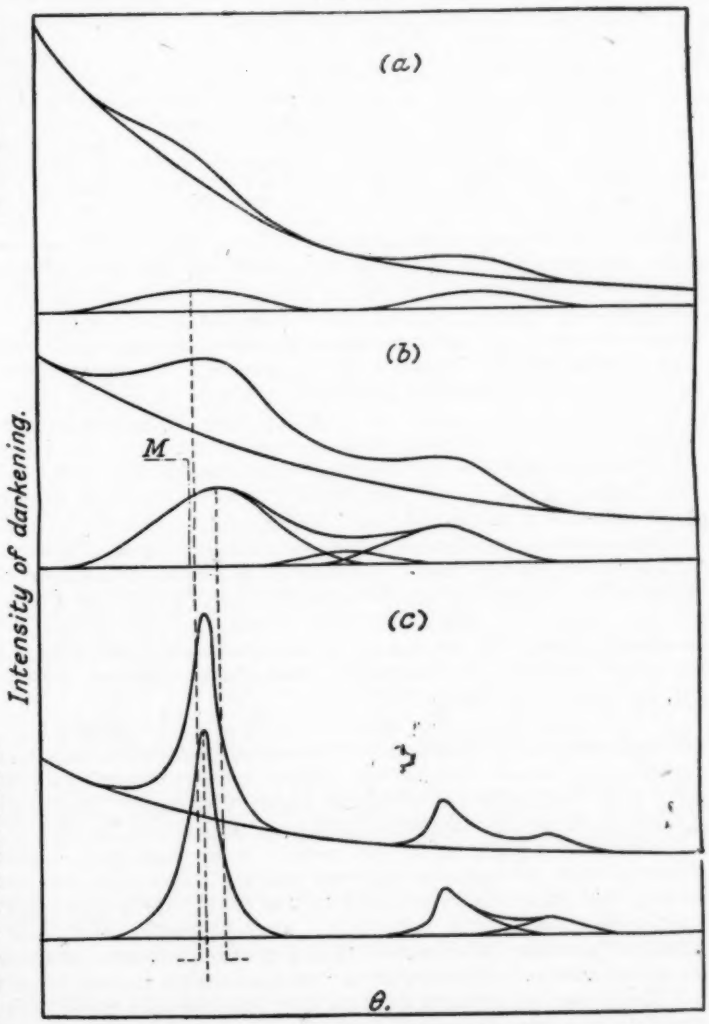


FIG. 3.



(*a*) *Cf. Plate* I*e*. (*b*) *Cf. Plate* I*f*. (*c*) *High temperature coke.*

The nature of hexaiodobenzene-carbon was sufficiently interesting to warrant further experimental work. It was thought possible that the rapidity of the decomposition of the hexaiodobenzene was in some way connected with the formation of the amorphous product. The method was not ideal owing to the difficulty of preparing hexaiodobenzene, the small yield of carbon obtained from it on carbonisation, and the corrosive action of the liberated iodine on the silica tube. Another method was therefore tried, *viz.*, by adding sodium amalgam, in small quantities at a time, to molten hexachlorobenzene kept at a temperature just below its b. p. (320°). The product was purified by water, dilute hydrochloric acid, and finally by heating to various temperatures in a stream of nitrogen to remove unchanged hexachlorobenzene and in vacuum to remove adsorbed

hydrogen chloride. Thus prepared, the carbons were voluminous, highly dispersed, black powders. Powder photographs were made of specimens which had been reheated to 500°, 800°, 1000° and 1200° in nitrogen; as far as could be judged the four photographs obtained were identical (see Plate I*f*). A typical small-scale micro-photometer trace is shown in Fig. 3*b*; it indicates a somewhat less disordered structure than that obtaining in the hexaiodobenzene-carbon, but it is different from the photometer traces of chars, cokes, etc. (see Fig. 3*c*). It differs in four important respects: (1) The maximum of the inner diffraction band is not in the position corresponding to its half-peak width, as judged from the photographs of chars and cokes: this is marked by *M* in Fig. 3*b*. (2) There are indications of the presence of an additional diffraction band between the 002 and the 100 diffraction. (3) The 100 diffraction gives a symmetrical trace, indicating that it is a three-dimensional and not a two-dimensional cross-lattice diffraction. (4) There is no sign of the 004 diffraction band.

The table below gives typical analyses, lattice parameters, and crystallite dimensions of carbons prepared by the above method and subsequently heated to various temperatures (see also Fig. 1*d*). The *a* dimensions

Carbonisation temp.	Percentage. C.	H.	O (diff.).	Cl.	Lattice parameter, A. *a*.	*c*/2.	Half-peak width, mm. 100'	002.	Crystallite dimension, A. *a*.	*c*.
400°	81·7	1·2	13·3	2·8	—	—	—	—	—	—
500	—	—	—	—	2·45	3·30	8·9	9·2	10·2	9·2
800	94·8	0·7	4·5	0·0	2·43	3·33	8·6	10·0	10·5	8·5
1000	96·2	0·5	3·3	0·0	2·42	3·34	8·5	10·0	10·6	8·5
1200	—	—	—	—	2·41	3·33	9·0	9·8	10·0	8·7

and the *a* spacings have been calculated by using Jones's formula and not Warren's, *i.e.*, it has been assumed that the 100 band is a three-dimensional and not a two-dimensional diffraction. The highly adsorptive character of the carbons made the interpretation of the analytical results difficult: the oxygen present is probably irreversibly adsorbed as water or atmospheric oxygen. The analytical results were, to some extent, dependent upon the thoroughness of the washing and thermal treatment in vacuum, but it was not possible to bring about further reductions in the percentage of oxygen. The constancy of both the *a* and the *c* dimensions is interesting and provides additional evidence of a rigid, cross-linked lattice structure. When heated to temperatures a little above 1200°, the carbons, as judged from their *X*-ray powder photographs, assumed a character more like that of cellulose chars.

It was thought possible that here, too, the velocity of reaction had an important effect in the formation of this type of carbon. Local overheating, involving perhaps large rises in temperature at the instant when the sodium amalgam was added to the molten hexachlorobenzene, probably occurred. There was definite evidence of momentary rapid reaction, which was occasionally accompanied by a flash of light if pure sodium instead of sodium amalgam was used. The reaction was made smoother and more controllable in the following manner. Freshly cut sodium was melted under medicinal paraffin in a bolt-head flask; small quantities of solid hexachlorobenzene were added from time to time, the temperature being kept at about 150—160°. Under these conditions the temperature may rise as high as 300° if the solid is added too quickly. The carbon and sodium chloride formed a crust on the surface of the molten sodium: it was broken periodically, and the sodium squeezed out by means of a glass rod.

The energetics of the reaction $C_6Cl_6 + 6Na = 6NaCl + 6C_{(solid)}$ suggest that it might be explosive. No explosions occurred either in these experiments or in those with sodium amalgam. When certain aliphatic halides were heated with molten sodium, however, even on a very small scale, violent explosions occurred: such mixtures should be considered highly dangerous. The smoothness of the reaction between hexachlorobenzene and sodium suggests that it does not involve the rupture of the aromatic ring system.

The carbons prepared by this method were thoroughly extracted and heated as described above. The *X*-ray powder photographs indicated that the *c* dimension was not altered by heating the product in nitrogen or in a vacuum to temperatures as high as 1000°: the *a* dimension, however, showed a distinct increase, reaching, in one experiment, a value of 16 A. after heating to 1000°: this growth was probably due to the presence of absorbed paraffin. Evidence in favour of this view was obtained by subjecting a sample in a high vacuum to a very slow rise of temperature: an appreciable amount of paraffin was collected in a liquid-air trap.

The above experiments indicate that the idea that black carbons, usually termed amorphous, are merely graphite in a very fine state of sub-division needs modification, although it is probably substantially correct in the case of certain carbons deposited from the gas phase (from either carbon monoxide or hydrocarbons). The nature of carbon prepared by carbonisation, *i.e.*, in the condensed phase, however, is influenced by the chemical and structural characterisitcs of the parent carbonaceous matter: cross-linking of the lamellar planes appears to be present, possibly brought about through the agency of oxygen atoms and also through the tilting of the aromatic hexagons. Although unequivocal evidence has not been obtained of the existence of the idealised structure shown in Plate II, yet there are indications that small disordered chunks of this type of structure may play a greater or a less part in building up chars and cokes. In this connection it is interesting to record that a specimen of a highly purified artificial graphite was recently found to give an *X*-ray powder photograph containing at least 16 faint sharp lines which cannot be indexed on the basis of either the Bernal or the Lipson structure: these lines also appear on the powder photographs of certain highly purified natural graphites. This concept of the two types of aromatic structure, *viz.*, the turbostratic lamellar and the disordered cross-linked, which build up the structure of chars and cokes, appears to offer a reasonable basis for explaining

the great range of properties shown by various carbons, *e.g.*, the highly specific nature and range of magnitude of adsorptive properties, the great variation of chemical reactivity, the subtle differences, quite apart from particle size, which determine the rubber-filling properties of carbon blacks; the differences in the tendency to graphitise at high temperatures; the differences in mechanical properties; the different degrees of atomic disorder which obtain in various carbons. The carbons prepared at low temperatures from hexachlorobenzene and sodium do not conduct electricity; they become electronic conductors after being heated to temperatures over 600°, in a similar manner to that shown by chars and cokes. The curves shown in Fig. 1 probably represent extreme types of crystallographic behaviour: intermediate behaviours are shown by other materials. The rapid increase in the *c* dimension between 800° and 1000° in the peat curve is perhaps an indication of a transition from the disordered cross-linked to the turbostratic lamellar type of structure.

Experimental.

Hexaiodobenzene was prepared by the method described by Rupp (*Ber.*, 1896, **29**, 1631). Benzoic acid (3 g.) was dissolved in fuming sulphuric acid (30 g.), heated to 120°, and iodine (20 g.) added in small quantities with continuous stirring, during ½ hour. After a further 6 hrs.' heating at 180°, the product was cooled and poured into cold water, and the solid formed was filtered off and heated on the water-bath to remove excess of iodine. Iodinated benzoic acid was extracted from the product by means of aqueous alkali, and the residue recrystallised from nitrobenzene. It formed reddish-brown needles, m. p. 340—360° (decomp.) (Found: I, 92·1. Calc. for C_6I_6: I, 91·36%). The product was carbonised in an atmosphere of oxygen-free nitrogen in an electrically-heated Vitreosil tube furnace.

Hexachlorobenzene crystals were melted in a 1 l. round-bottomed flask and then heated to about 320°; liquid sodium amalgam, prepared by grinding small pieces of freshly cut sodium with mercury, was added carefully, in small quantities at a time, the heating being continued throughout. The carbon liberated, mixed with the mercury and sodium chloride, formed in the middle of the flask a conglomerate, which was broken up from time to time. In order to avoid overheating the carbon, the addition of sodium amalgam was discontinued whilst a considerable excess of hexachlorobenzene still remained: some of this was removed by decantation. Most of the mercury liberated was also poured out of the flask. Water was then carefully added, followed by sufficient hydrochloric acid to neutralise the sodium hydroxide formed and leave the liquid faintly acid. The remainder of the mercury separated and was decanted. The carbon was washed thoroughly with hot water to remove the sodium chloride and the excess of hydrochloric acid, and then dried. The product still contained a large amount of unchanged hexachlorobenzene, which was removed by heating in a stream of nitrogen for an hour at 500°. The final vacuum heating was done in a fused quartz tube connected to a pumping system consisting of two stages of oil diffusion backed by a high-capacity rotary oil pump.

Carbon was also prepared from hexachlorobenzene as follows. To medicinal paraffin (B.P.) (100 c.c.) contained in a wide-necked bolt-head flask in an oil-bath, freshly cut sodium (about 7 g.) was added, and the whole heated to 150°. The sodium melted and formed a mercury-like layer. Hexachlorobenzene crystals, which are readily soluble in the paraffin, were added in small batches, about 90 mins. being taken to added 8 g. The mixture was stirred from time to time. The reaction, which proceeded slowly and quietly at about 150—160°, started with the tarnishing of the bright sodium surface and the gradual and progressive discoloration of the paraffin near the sodium surface. A jet-black deposit was quickly formed at the interface, which gradually formed a coherent incrustation, presumably consisting of a conglomerate of carbon and sodium chloride. This was periodically broken and squeezed by means of a glass rod, in order to expose a fresh sodium surface. Too rapid addition of the hexachlorobenzene led to a considerable rise in temperature. After being cooled, the reaction mixture was treated with rectified spirit followed by water, to remove the greater part of the excess sodium and the sodium ethoxide, hydroxide and chloride which had been formed. The product was then placed in a Soxhlet apparatus and thoroughly extracted with (*a*) dioxan (to remove paraffin and hexachlorobenzene), (*b*) water, and (*c*) alcohol: it was finally dried at 130°. Analysis of the product indicated that it still contained adsorbed impurities, and various modifications of the above treatment were tried, *e.g.*, a stage of prolonged steam-distillation, the exclusion of all organic solvents, a final treatment with a volatile solvent like ether, etc., but the results described above suggested that some paraffin remained in the product. For this reason the sodium amalgam method of preparing this type of carbon is preferable. The subsequent purification should be carried out with water (organic solvents should not be used), followed by thermal treatment in a high vacuum.

The *X*-ray powder photographs were made by using a cylindrical camera (radius 45·43 mm.) and cobalt-$K\alpha$ radiation. The electrical conductivity of the carbon samples was measured in a semimicro-apparatus consisting of a glass capillary tube carrying two closely fitting metal plungers. The conductivity measurements were made with the sample under high compression.

The above experiments were carried out in the Northern Coke Research Laboratory as part of the fundamental research programme of the British Coke Research Association.

King's College (University of Durham), Newcastle-upon-Tyne, 2. [*Received, November 28th*, 1945.]

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88. *Syntheses in the Indole Series. Part II. Derivatives of β-Keto-β-3-indolylpropionic Acid.*

By John W. Baker.

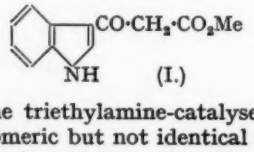
Indolylmagnesium iodide reacts with the acid chloride of the appropriate alkyl hydrogen malonate to give *methyl* (I) and *ethyl β-keto-β-3-indolylpropionate*, hydrolysis of which affords 3-indolyl methyl ketone (II). With nitrosyl chloride (I) affords its *oximino*-derivative, whilst with hydroxylamine it is converted into 3-3'-*indolyl*isoxazolid-5-one.

The complex action of phenyl *iso*cyanate on (I) and (II) has been investigated.

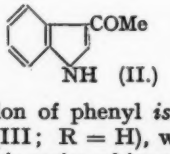
In continuation of the experimental study of possible intermediates in the enzymic breakdown of tryptophan to indole and verification of the tentative mechanism proposed by Baker and Happold (*Biochem. J.*, 1940, **36**, 657; Baker, Happold, and Walker, to be published in *Biochem. J.*, 1946) it became desirable to investigate

possible routes for the synthesis of tryptophan derivatives containing a β-keto-group. Condensation of suitable ester-acid chlorides with indolylmagnesium iodide (Baker, *J.*, 1940, 458) seemed to promise a suitable starting point for such syntheses.

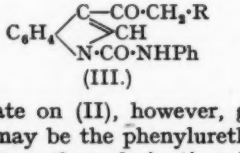
Condensation of indolylmagnesium iodide with the acid chloride of methyl hydrogen malonate affords, mainly, *methyl β-keto-β-3-indolylpropionate* (I), m. p. 120°, together with a small quantity of a *substance* $(C_{10}H_9ON)_x$, m. p. 204°, which is not identical with 3-indolyl methyl ketone since it is devoid of ketonic properties, and for which a molecular weight determination suggests the value $x = 2$. The structure of this by-product has not been ascertained. *Ethyl β-keto-β-3-indolylpropionate*, m. p. 121°, is similarly prepared from the acid chloride of ethyl hydrogen malonate. Hydrolysis of (I) either with boiling hydrochloric acid or with cold, aqueous sodium hydroxide followed by acidification at 0°, converts it into the genuine 3-indolyl methyl ketone (II), identical with a specimen synthesised by the action of indolylmagnesium iodide on acetyl chloride. The ketonic character of (I) is confirmed by the formation of a 2 : 4-*dinitrophenylhydrazone*, but an attempt to obtain an enolic derivative with phenyl *iso*cyanate led to complex products. No condensation occurred when the two substances were kept sealed together at room temperature for 24 hours. Addition of a few drops of triethylamine * to a hot solution of (I) and phenyl *iso*cyanate in dry benzene gave a *product*, m. p. 143° (decomp.), of composition approximating to the addition of two molecules of the *iso*cyanate to (I). In most solvents it formed a gel, attempts to purify which, gave a new *substance*, m. p. 170° (decomp.), containing only one molecule of phenyl *iso*cyanate per molecule of (I) and which may be (III; R = CO_2Me), since it was converted by dilute aqueous sodium hydroxide into a *derivative*, m. p. 237°, possibly (III; R = H), by hydrolysis of the β-keto-ester grouping.



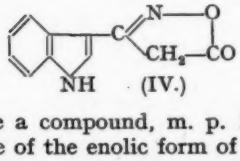
(I.)



(II.)



(III.)



(IV.)

The triethylamine-catalysed action of phenyl *iso*cyanate on (II), however, gave a compound, m. p. 152°, isomeric but not identical with (III; R = H), which may be the phenylurethane of the enolic form of (II). In view of the main object of this series of investigations, these derivatives have not so far been examined further.

Two routes for the introduction of an amino-group into (I) have been explored. Both give crude products which show slight positive results with tryptophanase but no pure product has yet been isolated. The action of nitrosyl chloride on an ethereal solution of (I) at 0° affords its β-iso*nitroso-derivative*, m. p. 155°, and an *isomeride*, m. p. 125—126° (decomp.). Reduction of the β-*iso*nitroso-derivative has, so far, yielded no pure product.

Ethyl β-keto-β-3-indolylpropionate is converted by one molecular proportion of bromine in dry ether into its *α-bromo-ester*, m. p. 132°, which reacts with a solution of ammonia in dry methyl alcohol, saturated at 0°, to give a bromine-free product, the structure of which has not yet been established.

With hydroxylamine hydrochloride and barium carbonate in boiling methyl alcohol (I) affords 3-3′-*indolyl*-iso*oxazolid-5-one* (IV), m. p. 192° (decomp.), a possible intermediate for the synthesis of β-amino-β-3-indolylpropionic acid.

Experimental.

Methyl β-Keto-β-3-indolylpropionate.—Indole (17·4 g.) dissolved in dry ether (100 c.c.) was added to the Grignard compound prepared from 3·6 g. of magnesium and 24 g. of ethyl iodide in 30 c.c. of dry ether and the mixture was refluxed on a steam-bath until the evolution of ethane ceased. The decanted solution of the indolylmagnesium iodide was added dropwise, with vigorous mechanical stirring, to a dry ethereal solution of 20·4 g. of the acid chloride of methyl hydrogen malonate, cooled in an ice-salt freezing mixture. After addition was complete the red reaction mixture was immediately decomposed with ice and ammonium chloride and was repeatedly extracted with ether.

Washing this orange-red solution with sodium carbonate solution removed most of the colour, and the resulting pale yellow ethereal solution was dried (Na_2SO_4) and the ether was distilled off through a Widmer column. The residue (23 g.) partly crystallised after keeping at room temperature for 48 hours, after which dilution with cold ether and filtration at the pump gave 5—7 g. of a clean, cream-coloured powder. This was repeatedly extracted (Soxhlet) with boiling benzene which left a small amount of insoluble material, m. p. 204°, after crystallisation from methyl alcohol (Found: C, 75·3; H, 5·85; N, 8·8; *M*, 375. $(C_{10}H_9ON)_2$ requires C, 75·5; H, 5·7; N, 8·8%; *M*, 312).

Concentration of the benzene solution gave *methyl β-keto-β-3-indolylpropionate*, m. p. 120° after recrystallisation from the same solvent (Found: C, 66·5; H, 5·2; N, 6·55. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·45%).

Its dark red 2 : 4-*dinitrophenylhydrazone*, crystallised from acetone, had m. p. 262° (decomp.) (Found: C, 54·1; H, 3·9. $C_{18}H_{15}O_8N_5$ requires C, 54·4; H, 3·8%).

Ethyl β-keto-β-3-indolylpropionate, m. p. 121°, was similarly prepared (Found: C, 67·9; H, 6·1. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·6%). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 255°, after crystallisation from acetone (Found: C, 55·55; H, 4·14; N, 17·1. $C_{19}H_{17}O_8N_5$ requires C, 55·45; H, 4·2; N, 17·0%).

A mixture of the methyl keto-ester (I) (0·55 g.) and phenyl *iso*cyanate (2 mols., 0·6 g.) was warmed in 5—10 c.c. of dry benzene until an almost homogeneous solution was obtained, and then a few drops of triethylamine were added. The solution was again warmed on a steam-bath for a few minutes and seeded with the product. Crystallisation began on keeping at room temperature, but the whole mass soon set to a gel. After 24 hours the mass was drained on porous porcelain in a desiccator and the powdered *product* was triturated with ether. A specimen, m. p. 143° (decomp.), was analysed (Found: C, 69·1; H, 5·4; N, 9·5. $C_{26}H_{31}O_5N_3$ requires C, 68·6; H, 4·6; N, 9·2%). Attempts to purify this specimen further by "crystallisation" from acetone gave a *product* which, after washing with a warm mixture of acetone–

* The efficacy of base catalysis in the condensation of phenyl *iso*cyanate with alcohols has been demonstrated in a series of kinetic investigations, the results of which will be published later.

ether, had m. p. 170° (decomp.) (Found: C, 67·4; H, 5·1; N, 8·9. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3%). This was warmed with a few c.c. of 2N-sodium hydroxide and then kept for 24 hours at room temperature. The white crystalline material was filtered, washed, and crystallised from methyl alcohol. The product, m. p. 237°, depressed the m. p. of carbanilide (m. p. 240°) to 210—220°, and analysis suggests that it is the N-*phenylcarbamido*-derivative (III; R = H) of 3-indolyl methyl ketone (Found: C, 73·1; H, 4·9. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·0%).

Hydrolysis of the Keto-ester.—The keto-ester (0·22 g.) was kept, with frequent shaking, with 3 c.c. of cold, 0·5N-sodium hydroxide, filtered from a trace of undissolved material, and then added slowly to 3 c.c. of ice-cold 0·5N-sulphuric acid. The heavy white precipitate was filtered off and washed with water. The filtrate gave a pale purple colour with ferric chloride. Crystallisation of the dried precipitate from methyl alcohol gave 3-indolyl methyl ketone, m. p. 194°, not depressed by admixture with a synthetic specimen prepared (below) by the action of indolylmagnesium iodide on acetyl chloride (Found: C, 75·15; H, 5·8. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·7%). The same ketone was obtained by ether extraction of the product resulting from hydrolysis of the keto-ester with boiling, concentrated hydrochloric acid under reflux for 1—2 hours, but much tar formation also occurs under these conditions. The ketone, m. p. 194°, depresses the m. p. of the compound $(C_{10}H_9ON)_2$, m. p. 204° (obtained in the original preparation of the keto-ester), to 167°. Moreover, the latter compound gives no precipitate with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid solution.

3-3′-*Indolylisooxazolid-5-one.* The keto-ester (I) (0·5 g.) was refluxed with hydroxylamine hydrochloride (0·2 g.) and pure barium carbonate (0·25 g.) in dry methyl alcohol (10 c.c.) for 24 hours. After cooling and filtering, the solution was concentrated to small bulk and allowed to crystallise. After twice recrystallising from methyl alcohol the *isooxazolidone* was obtained in long slender prisms, m. p. 192° (decomp.) after darkening at *ca.* 182° (Found: 65·7; H, 4·10; N, 13·7. $C_{11}H_9O_2N_2$ requires C, 66·0; H, 4·0; N, 14·0%).

Methyl α-Oximino-β-keto-β-3-indolylpropionate.—Methyl β-keto-β-3-indolylpropionate (0·55 g.) was suspended in 10—15 c.c. of dry ether, the suspension was cooled in ice, and a stream of nitrosyl chloride (from nitrosylsulphuric acid and sodium chloride) was passed in for 10—15 minutes with frequent stirring. The insoluble cream coloured powder was separated by filtration from the orange-red solution. The powder was washed with dry ether; it was insoluble in most solvents. A specimen, m. p. 125—126° (decomp.), was analysed (Found: C, 57·3; H, 4·1. $C_{12}H_{10}O_4N_2$ requires C, 58·5; H, 4·1%). It is thus probably isomeric with the *oximino* compound which was obtained by evaporation of the ethereal filtrate under reduced pressure at room temperature. This crystallised from ether in felted masses of fine needles, m. p. 155° (Found: N, 11·2. $C_{12}H_{10}O_4N_2$ requires N, 11·4%).

Synthesis of 3-*Indolyl Methyl Ketone.*—The Grignard reagent prepared from 0·8 g. of magnesium and 5·4 g. of ethyl iodide was warmed with 3·9 g. of indole in dry ether solution until evolution of ethane ceased. The product was added dropwise to a solution of 2·6 g. of acetyl chloride in dry ether, cooled in a freezing mixture, with constant stirring. The product was decomposed with ice and ammonium chloride and extracted with ether. The residue from the dried ethereal solution was repeatedly extracted with boiling ligroin (b. p. 40—60°) to remove any unchanged indole, and the insoluble residue was extracted with ether. The portion undissolved by the ether was crystallised from benzene containing a little ethyl alcohol. 3-Indolyl methyl ketone, m. p. 194°, separated. The portion extracted with ether was evaporated, and the residue, after several crystallisations from benzene, gave 1 : 3-diacetylindole, m. p. 152° (Found: C, 71·7; H, 5·8; N, 7·4. Calc. for $C_{12}H_{11}O_2N$: C, 71·6; H, 5·5; N, 7·0%) (cf. Oddo and Sessa, *Gazzetta*, 1911, **41**, i, 239).

Action of Phenyl iso*Cyanate on* 3-*Indolyl Methyl Ketone.*—A few drops of triethylamine were added to a hot solution of 0·3 g. of the ketone and 0·4 g. of phenyl *iso*cyanate in 10 c.c. of dry benzene and the mixture was kept sealed at room temperature for 18 hours. The solid product was separated and crystallised from dry benzene. Carbanilide separated first, and from the mother liquor by repeated recrystallisation from benzene was obtained a *substance*, m. p. 154° with previous softening (Found: C, 73·5; H, 5·2; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·0; N, 10·1%).

Bromination of Ethyl β-Keto-β-3-indolylpropionate.—A solution of dry bromine (1·2 g.) in ether was added dropwise to a cold suspension of 1·74 g. of the keto-ester in the same solvent with constant stirring. The solution was evaporated over potassium hydroxide in a vacuum desiccator at room temperature until the residue was free from hydrogen bromide. The *bromo-ester* had m. p. 133° after several crystallisations from ether (Found: C, 50·3; H, 4·2; Br, 25·85. $C_{13}H_{12}O_3NBr$ requires C, 50·3; H, 3·9; Br, 25·8%).

Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

THE UNIVERSITY, LEEDS. [*Received, December 7th*, 1945.]

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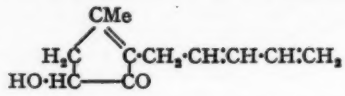
89. *The Structure of Pyrethrolone and Related Compounds. Part V.*

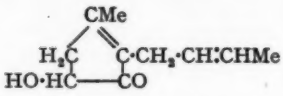
By T. F. WEST.

Using the method of LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 106) five semicarbazones have been obtained from the mixture of ketones known as "pyrethrolone" derived from Kenya pyrethrum flowers. By a modified procedure it was possible to isolate a sixth semicarbazone corresponding to the inactive modification of pyrethrolone C-1 and to offer an explanation for discrepancies in the melting points recorded for different samples of pyrethrolone B-1 semicarbazone. The absorption data for the semicarbazones and their hydrogenation products are in accord with the structures (I) and (II) proposed for the two ketones which are present in "natural pyrethrolone" as dextro and racemic forms (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114).

SPECTROGRAPHIC study of the pyrethrins and related compounds (Gillam and West, *J.*, 1942, 671; 1944, 49) raised considerable difficulties in connection with the accepted ideas on the structure of these compounds and an explanation was sought for the anomalous chemical reactions of the *cyclo*pentenolone fragment (West, *J.*, 1944, 51, 239, 642; 1945, 412). Meanwhile LaForge and Barthel subjected pyrethrolone to an exhaustive examination to detect heterogeneity and finally succeeded in isolating no fewer than five semicarbazones by combining a process of fractionation and acetylation before converting the fractions into semicarbazones (*J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106, 114, 222). These lævo-rotatory and inactive semicarbazones were considered to correspond to dextro and racemic forms of the ketone of empirical formula $C_{11}H_{14}O_2$ (pyrethrolone) with smaller quantities of *d*- and *dl*-forms of (II) (cinerolone). The semicarbazones A-1 and A-2 were derived from the *d*- and the *dl*-form respectively of cinerolone, B-1 and B-2 from the *d*- and the *dl*-form of one possible geometric isomer of pyrethrolone, and C from the *d*-form of the second possible geometric isomer of pyrethrolone. The preparation of the *dl*-form of the semicarbazone of pyrethrolone C is described below, and

now that all the possibilities (except the enantiomorphs of A-1, B-1 and " C ") have been isolated the terms C-1 and C-2 are used in this paper to avoid misunderstanding.

(I.) 

 (II.)

Structure (I) was first suggested by Gillam and West (*loc. cit.*) for " pyrethrolone," but the production on ozonolysis of acetaldehyde with only small proportions of formaldehyde raised serious difficulties. LaForge and Barthel surmounted these difficulties by arguments based upon their discovery of the heterogeneous nature of pyrethrolone. By treatment with thionyl chloride, cinerolone was converted into the 5-chloro-derivative. This was reduced to the deoxy-derivative, cinerone, and dihydrocinerone was shown to be identical with synthetic 3-methyl-2-butyl*cyclo*pent-2-en-1-one. LaForge and Barthel (*loc. cit.*) considered that the terminal methyl values—which appear, however, to give results difficult to interpret (West, *J.*, 1945, 412)—and the absorption data confirmed that in cinerolone the side-chain double bond was in the 2 : 3 and not the 1 : 2 position, whilst for the pyretholone constituents ($C_{11}H_{14}O_2$) the evidence was considered to confirm formula (I).

In view of the repercussions involved in the discovery that pyrethrins I and II are such complex mixtures it appeared desirable to repeat this work and to supplement the absorption data recorded. Each of the five semicarbazones described by LaForge and Barthel has been prepared from " pyrethrolone " derived from pyrethrin concentrates including those predominating in pyrethrin I and pyrethrin II respectively, although the proportion of the various semicarbazones isolated showed some variation. From observations made in a number of experiments the semicarbazone of pyrethrolone B-1 has m. p. 210° (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114) and the product m. p. 213—215° obtained by strict adherence to the LaForge and Barthel

*Absorption Spectra (Alcoholic Solutions) and Terminal Methyl Numbers * for the Semicarbazones of Cinerolone A-1 and A-2 and Pyrethrolone B-1, B-2, C-1, and C-2 and Hydrogenated Products.*

	$\lambda_{max.}$ A.	ε.	Me (C), %.	Terminal methyl number.*	M.W. used.
Samples of semicarbazones derived by acetate method.					
Cinerolone acetate A-1	2660	22,900	16·3	2·88	265
Cinerolone acetate A-2	2660	20,250	16·4	2·90	265
Pyrethrolone acetate B-1	2290 2665	21,800 19,700	12·9	2·38	277
Pyrethrolone acetate B-2	2295 2650	15,650 15,000	13·5	2·49	277
Pyrethrolone acetate C-1	2310 2660	22,000 16,400	11·8	2·18	277
Pyrethrolone acetate C-2	2310 2670	21,500 15,500	11·4	2·10	277
Cinerolone A-1	2660 (2320) no band	18,300 10,900	12·1	1·80	223
Cinerolone A-2	2660 (2320) no band	17,000 10,200	12·2	1·82	223
Pyrethrolone B-1	2320 2665	18,700 17,600	8·9	1·40	235
Pyrethrolone B-2	2310 2650	24,300 18,200	9·2	1·44	235
Pyrethrolone C-1	2310 2665	25,350 19,800	7·6	1·19	235
Pyrethrolone C-2	2310 2660	24,000 19,600	8·0	1·25	235
Dihydrocinerolone A-1	2650	21,800	13·2	1·98	225
Dihydrocinerolone A-2	2650	17,700	12·2	1·83	225
Tetrahydropyrethrolone B-1	2650	16,800	11·4	1·82	239
Tetrahydropyrethrolone B-2	2650	22,000	12·9	2·05	239
Tetrahydropyrethrolone C-1	2650	22,700	12·8	2·03	239
Tetrahydropyrethrolone C-2	2650	22,000	12·5	1·99	239
Samples of semicarbazones derived by fractional distillation of natural pyrethrolone.					
Cinerolone A-1	2650 (2300)	19,600 9,030	12·0	1·78	223
Pyrethrolone B-1	2300 2650	20,350 19,200	9·3	1·46	235
Pyrethrolone C-1	2300 2655	24,900 18,900	9·2	1·44	235
Dihydrocinerolone A-1	2650	18,800	13·0	1·95	225
Tetrahydropyrethrolone B-1	2650	20,600	12·1	1·93	239
Tetrahydropyrethrolone C-1	2650	21,000	12·6	2·01	239

* Barthel and LaForge, *Ind. Eng. Chem. Anal.*, 1944, **16**, 434.

method is a mixture of the semicarbazones of pyrethrolone B-1 and pyrethrolone C-1. The sixth semicarbazone (pyrethrolone semicarbazone C-2) corresponding to the racemic form of the dextrorotatory pyrethrolone C-1 was isolated by applying the acetate separation to an appropriate fraction, and a mixture of m. p. 213—214° corresponding to the impure B-1 semicarbazone was obtained as a by-product. By rigorous fractional distillation of " natural pyrethrolone " the three optically active forms of the semicarbazones were prepared without previous acetylation, so that no changes in the position of the double bonds in the molecules appeared to have taken place during treatment with acetic anhydride or subsequent conversion into the semicarbazones of the corresponding *cyclo*pentenolones. The semicarbazones (A-1 and A-2) of cinerolone absorbed approximately one molecular proportion, and the semicarbazones of pyrethrolones B-1, B-2, C-1, and C-2 approximately two molecular proportions, of hydrogen to give dihydro- and tetrahydro-derivatives respectively of which the absorption spectra were typical of semicarbazones derived from αβ-unsaturated ketones (Gillam and West, *J.*, 1942, 486; Evans and Gillam, *J.*, 1943, 565).

The cinerolones appeared to be present to the extent of about 20—30% in the samples of " natural pyrethrolone " examined. The data recorded in the experimental part confirm the work of LaForge and Barthel, and the absorption data in the table are in accord with the structures which they propose for the two *cyclo*pentenolones of empirical formulæ $C_{10}H_{14}O_2$ and $C_{11}H_{14}O_2$. The semicarbazones of the cinerolones showed maximum absorption at 2655±5 A. (Evans and Gillam, *loc. cit.*), whilst the various pyrethrolone semicarbazones had maxima at 2655±5 A. corresponding with the $>C{=}C{-}C{=}N-$ linkage and in addition another band at 2310±10 A. due to the separate conjugated diene chromophore system present in the side chain (Gillam and West, *loc. cit.*).

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Separation of Pyrethrolones and Cinerolones through the Acetates.—Pyrethrum extract containing pyrethrin I 48·0%, pyrethrin II 43·8% (Seil method), acid value 2 (Barthel, Haller, and LaForge, *Soap*, 1944, **20**, No. 7, 121), having $\lambda_{max.}$ 2295 A. with $E^{1\%}_{1\,cm.}$ 765 (in alcohol) (370 g.), gave crude mixed pyrethrin semicarbazones (420 g.) containing some non-crystalline material. This yielded 230 g. of crude pyrethrolone semicarbazone, Me(C), 11·3%, which was recrystallized to give pyrethrolone semicarbazone (182 g.), m. p. 204—205°, Me(C), 9·2%, leaving a residue (31 g.) insoluble in methyl alcohol. The regenerated pyrethrolone (128 g.) had b. p. 131—150°/1·2 mm., $n_D^{20°}$ 1·5372, $\alpha_D^{20°}$ 13·6°, Me(C), 13·2%. This was distilled to give two fractions: (a) (65 g.), b. p. 128—140°/1 mm., $n_D^{20°}$ 1·5366, $\alpha_D^{20°}$ 13·8°, Me(C), 13·9%, (b) (26 g.), b. p. 140—147°/1 mm., $n_D^{20°}$ 1·5410, $\alpha_D^{20°}$ 12·4°. Proceeding essentially as described by LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 106) fraction (a) (61·5 g.) was acetylated and by distillation two fractions were obtained: (22·3 g.), b .p. 96—101°/0·35 mm., $n_D^{27°}$ 1·4978, α_D 24·8°, Me(C), 21·2%, and (37·5 g.), b. p. 110—118°/0·4 mm., $n_D^{27°}$ 1·5110, α_D 29·7°, Me(C), 17·5%. Cinerolone acetate semicarbazone A-1 had m. p. 148—151° (Found: C, 59·1; H, 7·1%). Cinerolone acetate semicarbazone A-2 had m. p. 150—152° (Found: C, 59·3; H, 7·1%). Pyrethrolone acetate semicarbazone B-1 had m. p. 122—124° (Found: C, 59·1, 59·2; H, 7·0, 6·75%). Pyrethrolone acetate semicarbazone B-2 had m. p. 168—170° (Found: C, 60·45; H, 7·0. Calc. for $C_{13}H_{19}O_3N_3$: C, 58·9: H, 7·2. Calc. for $C_{14}H_{19}O_3N_3$: C, 60·65; H, 6·9%). Cinerolone semicarbazone A-1 had m. p. 202—203°, $[\alpha]_D$ −186° (*c*, 1 in pyridine) (Found: C, 59·8; H, 7·5%). Cinerolone semicarbazone A-2 had m. p. 199—200°, $[\alpha]_D$ ±0° (*c*, 1 in pyridine) (Found: C, 59·5; H, 7·45%). Pyrethrolone semicarbazone B-1 had m. p. 213—215°, $[\alpha]_D$ −182° (*c*, 1 in pyridine) (Found: C, 60·7; H, 7·4%). Pyrethrolone semicarbazone B-2 had m. p. 207—208°, $[\alpha]_D$ ±0° (*c*, 0·5 in pyridine) (Found: C, 60·8; H, 7·3%). A pyrethrolone fraction b. p. 135—137°/0·5 mm., $n_D^{20°}$ 1·5530, $\alpha_D^{18°}$ 11·2°, Me (C), 12·5%, was obtained by fractionating (b) above (LaForge and Barthel, *loc. cit.*) and was used to prepare the C-1 semicarbazone, m. p. 219—220° (decomp.), $[\alpha]_D$ −155° (*c*, 0·2 in pyridine) (Found: C, 61·2; H, 6·7. Calc. for $C_{11}H_{17}O_3N_3$: C, 59·2; H, 7·6. Calc. for $C_{12}H_{17}O_3N_3$: C, 61·3; H, 7·2%). The data given in the table refer to these particular samples and to their hydrogenation products (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114), the properties of which were: the A-1 semicarbazone (0·4 g.) hydrogenated in methyl alcohol using a platinum oxide catalyst absorbed 40 ml. of hydrogen at N.T.P. (Calc. for $C_{11}H_{17}O_3N_3$, one double bond: 40·2 ml.) and the recrystallised *l*-dihydrocinerolone A-1 semicarbazone had m. p. 196—197°, $[\alpha]_D$ −205° (*c*, 1 in pyridine) (Found: C, 59·1; H, 8·4. Calc. for $C_{11}H_{19}O_3N_3$: C, 58·7; H, 8·4%). The A-2 semicarbazone (0·2 g.) absorbed 20·2 ml. of hydrogen at N.T.P. (Calc. 20·1 ml.) to give *i*-dihydrocinerolone A-2 semicarbazone, m. p. 184—185°, $[\alpha]_D$ ±0° (*c*, 1 in pyridine) (Found: C, 59·5; H, 8·7%). The B-1 semicarbazone (0·4 g.) absorbed 76 ml. of hydrogen at N.T.P. (Calc. for $C_{13}H_{17}O_3N_3$, two double bonds: 76·3 ml.) to give the *l*-tetrahydrosemicarbazone, m. p. 195—197°, $[\alpha]_D$ −196° (*c*, 1 in pyridine). The B-2 semicarbazone (0·2 g.) absorbed 38 ml. of hydrogen at N.T.P. to give the *i*-tetrahydrosemicarbazone, m. p. 172—174°, $[\alpha]_D$ ±0° (*c*, 1 in pyridine). The C-1 semicarbazone (0·2 g.) absorbed 38 ml. at N.T.P. to give the *l*-tetrahydrosemicarbazone, m. p. 195—197° (not depressed on admixture with tetrahydropyrethrolone B-1 semicarbazone), $[\alpha]_D$ −209° (*c*, 1 in pyridine). The process was repeated starting with a pyrethrum concentrate containing pyrethrin I, 76·0, pyrethrin II, 21·5% (Seil) to give the following semicarbazones: A-1, A-2, B-1, B-2, and C-1 with m. p. 202—203°, 199—200°, 207—208°, 207—208°, and 217—218°, and $[\alpha]_D$ (*c*, 1 in pyridine) −199°, +0·9°, −194°, −1·2°, and −167° respectively. Starting with a concentrate containing pyrethrin I, 12·7, pyrethrin II, 78·8% (Seil) the semicarbazones, A-1, A-2, B-1, B-2, and C-1 had m. p. 202—203°, 199—200°, 208—210°, 207—208°, and 217—219°, and $[\alpha]_D$ (*c*, 1 in pyridine) −201°, ±0°, −186°, −1·4°, and −165° respectively. In another experiment a pyrethrum concentrate (345 g.) (pyrethrin I, 49·0%, pyrethrin II, 43·5%) gave semicarbazones as follows: A-1 (14·5 g.), A-2 (1·8 g.), B-2 (5 g.), m. p. 202—203°, 199—200°, and 207—208°, and $[\alpha]_D^{20°}$ (*c*, 1 in pyridine) −192°, ±0°, and −5° respectively. The pyrethrolone acetate fraction, $n_D^{20°}$ 1·5127, $\alpha_D^{25°}$ 26·4°, corresponding to the B-1, B-2 mixture gave (after removing the B-2 semicarbazone) by evaporating the benzene liquors a product which was separated by recrystallisation from dry ether into a crystalline portion and a syrupy portion (obtained on evaporating the ether liquors to dryness) in about equal amounts. (The ether-insoluble resinous material was rejected.) The crystalline material had m. p. 118—120°. On saponification the pyretholone B-1 semicarbazone obtained had m. p. 210—211°, $[\alpha]_D$ −187° (*c*, 1 in pyridine). The non-crystalline portion on saponification gave pyrethrolone B-1 semicarbazone, m. p. 206—207°, $[\alpha]_D$ −185° (*c*, 1 in pyridine). Each of these semicarbazones absorbed 2 mols. of hydrogen to give tetrahydroderivatives, m. p. and mixed m. p. 194—195°, and $[\alpha]_D$ −188° and −208° (*c*, 1 in pyridine), respectively. (The constants for the B-1 semicarbazone appeared to depend upon the refractive index of the acetate fraction used. The B-1 pyrethrolone semicarbazone, m. p. 213—215°, obtained in the first experiment was derived from an acetate fraction $n_D^{20°}$ 1·5143.)

The "pyrethrolone C fraction" derived from the pyrethrin I concentrate had b. p. 133—134°/0·4 mm., $n_D^{20°}$ 1·5520, $a_D^{25°}$ 5·6°, whilst that from the pyrethrin II concentrate had b. p. 134—135°/0·4 mm., $n_D^{20°}$ 1·5511, $a_D^{25°}$ 9·3°. In an experiment the "pyrethrolone C-fraction" obtained by fractionation as described by LaForge and Barthel had b. p. 142—144°/0·8 mm., $n_D^{20°}$ 1·5520, a_D 10·2°, semicarbazone m. p. 218—219°, $[\alpha]_D^{20°}$ −162° (*c*, 1 in pyridine). The fraction (12 g.) from which this was derived (b. p. 142—150°/1 mm., $n_D^{20°}$ 1·5415, $a_D^{25°}$ 13°) was acetylated. The acetylated product gave a semicarbazone (12 g.) which was accompanied by sticky material. The portion insoluble in cold benzene (3·1 g.) after two recrystallisations from hot benzene gave pyrethrolone C-2 acetate semicarbazone (1·3 g.), m. p. 163—165°, $[\alpha]_D$ ±0° (*c*, 1·25 in methyl alcohol) (Found: C, 61·1; H, 6·7. Calc. for $C_{14}H_{19}O_3N_3$: C, 60·65; H, 6·9%). The portion (9·7 g.) recovered by evaporating the cold benzene solution, after recrystallisation from ether, gave pyrethrolone C-1 acetate semicarbazone (3 g.), m. p. 128—130°, $[\alpha]_D$ −47·8° (*c*, 2·5 in methyl alcohol), −32·6° (*c*, 1 in pyridine) (Found: C, 59·7; H, 6·9%). A resinous material (3·4 g.) insoluble in ether was rejected. From the ether filtrates a syrupy product (3·3 g.) was produced (cf. B-1, B-2 mixture). The inactive acetate semicarbazone on saponification in the usual manner gave pyrethrolone C-2 semicarbazone, m. p. 216—217° (rapid heating), $[\alpha]_D^{20°}$ −1° (*c*, 1 in pyridine) (Found: C, 61·5; H, 7·2. Calc. for $C_{12}H_{17}O_2N_3$: C, 61·3; H, 7·2%). When hydrogenated in the presence of a reduced platinum oxide catalyst this semicarbazone (0·2 g.) absorbed 37·8 ml. of hydrogen at N.T.P. (Calc. for $C_{12}H_{17}O_2N_3$, two double bonds: 38·1 ml.) to give an inactive tetrahydro-derivative, m. p. 171—173° (not depressed on admixture with the semicarbazone of tetrahydropyrethrolone B-2), $[\alpha]_D$ ±0° (*c*, 1 in pyridine) (Found: C, 60·5; H, 8·8. Calc. for $C_{12}H_{21}O_2N_3$: C, 60·25; H, 8·8%). The pyrethrolone C-1 acetate semicarbazone gave on saponification pyrethrolone C-1 semicarbazone, m. p. 219—220°, $[\alpha]_D^{20°}$ −159° (*c*, 1 in pyridine), identical with the semicarbazone of pyrethrolone C-1 prepared from "pyrethrolone" by fractionation and (0·2 g.) absorbed 37·9 ml. of hydrogen at N.T.P. to give tetrahydropyrethrolone C-1 semicarbazone, m. p. 195—196°, $[\alpha]_D^{20°}$ −195° (*c*, 1 in pyridine). The syrupy product on saponification gave a semicarbazone, m. p. 213—214°, not depressed by admixture with the semicarbazone B-1, m. p. 213—215°, obtained in the first experiment, $[\alpha]_D^{20°}$ −178° (*c*, 1 in pyridine). (This suggests that the B-1 semicarbazone previously obtained by LaForge and Barthel was a mixture of pyrethrolone B-1 semicarbazone, m. p. 210—211°, and pyrethrolone C-1 semicarbazone, m. p. 219—220°.) This product (0·2 g.) absorbed 38·3 ml. of hydrogen at N.T.P. to give a tetrahydro-derivative, m. p. 195—196° (unchanged on admixture with tetrahydropyrethrolone B-1 semicarbazone), $[\alpha]_D$ −208° (*c*, 1 in pyridine).

Constituents from "Pyrethrolone" by Fractionation.—"Natural pyrethrolone," on rigorous fractional distillation at 0·5 mm., gave (i) b. p. 122—124°/0·7 mm., $n_D^{20°}$ 1·5221, $[\alpha]_D$ 12·6°, Me (C), 15·7%; (ii) b. p. 135—137°/0·7 mm., $n_D^{20°}$ 1·5402, $[\alpha]_D$ 14·6°, Me (C), 12%; (iii) b. p. 140—142°/0·9 mm., $n_D^{20°}$ 1·5505, $[\alpha]_D$ 11·4°, Me (C), 12·4%. (During the fractionation the refractive index of intermediate fractions rose steadily with rise in b. p. whilst the optical rotation rose to a maximum and then decreased.) The semicarbazones derived from fractions (i), (ii) and (iii) correspond with the cinerolone A-1, pyrethrolone B-1 (contaminated with pyrethrolone B-2) and pyrethrolone C-1 semicarbazone obtained by the acetate method and had the following properties: A-1, m. p. 200—201°, $[\alpha]_D$ −180° (*c*, 1 in pyridine) (Found: C, 59·4; H, 7·6%). B-1, m. p. 208—209°, $[\alpha]_D$ −167° (*c*, 1 in pyridine) (Found: C, 60·9; H, 7·2%). C-1, m. p. 218—219°, $[\alpha]_D$ −152° (*c*, 0·16 in pyridine) (Found: C, 61·1; H, 7·25%). Cinerolone A-1 semicarbazone (0·2 g.) absorbed 22·2 ml. of hydrogen at N.T.P. to give dihydrocinerolone A-1 semicarbazone, m. p. 196—197°, $[\alpha]_D^{20°}$ −220° (*c*, 1 in pyridine). Pyrethrolone B-1 semicarbazone (0·4 g.) absorbed 76·1 ml. of hydrogen at N.T.P. to give the tetrahydro-derivative, m. p. 195—197°, $[\alpha]_D^{20°}$ −196° (*c*, 1 in pyridine), and pyrethrolone C-1 semicarbazone (0·2 g.) absorbed 38·2 ml. of hydrogen at N.T.P. to give the tetrahydro-derivative, m. p. 195—197°, $[\alpha]_D^{20°}$ −207° (*c*, 1 in pyridine). The m. ps. were not depressed on admixture with the corresponding derivatives obtained *via* the acetates.

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90. *Substances Allied to Benzylamine-p-sulphonamide.*

By T. Dewing.

Homologues of di-(*p*-aminophenyl) sulphone have been made incorporating benzylamine groups. These are much less active against *Cl. Welchii* than is benzylamine-*p*-sulphonamide, and furnish additional evidence that the mode of action of this series is different from that of the sulphanilamides.

The recent revival of interest in benzylamine-*p*-sulphonamide, owing to its effectiveness against gas gangrene infections when applied locally, has led to the preparation of a number of compounds of the general type $NR'R''\cdot CH_2\cdot C_6H_4\cdot SO_2R$, many of which show activity against *Cl. Welchii*. The evidence available suggests that the mode of action of this series of drugs is different from that of the sulphanilamide series. Thus the N^1-thiazole and N^1-pyrimidine derivatives of benzylamine-*p*-sulphonamide (Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1458) were found by Hamré (*Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 110) to be practically inactive and, whilst *p*-aminomethylphenyl methyl sulphone, $NH_2\cdot CH_2\cdot C_6H_4\cdot SO_2\cdot Me$, and *p*-guanylphenyl methyl sulphone, $NH_2\cdot(NH{:})C\cdot C_6H_4\cdot SO_2\cdot Me$, are effective drugs (Evans, Fuller, and Walker, *Lancet*, 1944, II, 523), *p*-aminophenyl methyl sulphone in the sulphanilamide series is inactive (Buttle, Dewing, *et al.*, *Biochem. J.*, 1938, **32**, 1101). Moreover the action of benzylamine-*p*-sulphonamide is not inhibited by *p*-aminobenzoic acid or by *p*-aminomethylbenzoic acid (Goldacre, *Nature*, 1944, **154**, 796).

In view of the higher activity shown by di-(*p*-aminophenyl) sulphone against streptococci compared with sulphanilamide, it was decided to prepare homologues of the former compound. Of these, *di-*(p-*aminomethylphenyl*) *sulphone* is of very feeble activity against *Strep. Pyogenes* and against *Cl. Welchii*, being much inferior to benzylamine-*p*-sulphonamide against the latter organism, but its activity is not inhibited by *p*-aminobenzoic acid or by *p*-aminomethylbenzoic acid. p-*Aminophenyl* p-*aminomethylphenyl sulphone* has no activity against *Cl. Welchii*, but shows good activity against streptococci which is inhibited by *p*-aminobenzoic acid. This compound is therefore a typical member of the sulphanilamide series and the introduction of a *p*-aminomethyl group has had no qualitative effect on its activity. Confirming the results of Goldacre (*loc. cit.*) it was found that *p*-aminomethylbenzoic acid had no inhibitory effect on the action of benzylamine-*p*-sulphonamide, although it had quite a definite inhibitory effect on the action of the sulphanilamides.

Experimental.

p-Aminomethylbenzoic Acid, $NH_2 \cdot CH_2 \cdot C_6H_4 \cdot CO_2H$.—This was originally prepared by Gunther (*Ber.*, 1890, **23**, 1060) by a rather lengthy method and more recently a simpler preparation has been described (Albert and Magrath, *J.*, 1944, 678). The following method was used by the author:

p-Tolyl cyanide was readily obtained in excellent yield from *p*-toluidine by the Sandmeyer method using sodium nickel cyanide, and on bromination *p*-bromomethylphenyl cyanide (Bense, *Ber.*, 1894, **27**, 2169) was obtained. This compound was lachrymatory and irritant to the skin. *p*-Bromomethylphenyl cyanide (5 g.) was boiled with concentrated hydrochloric acid (35 ml.) and water (15 ml.) for 30 hours. The material at first became oily and later resolidified. The solid was dissolved in 5% sodium carbonate solution (60 ml.), decolorised with charcoal, and the acid, m. p. 220°, precipitated with hydrochloric acid. Salkind (*Centr.*, 1914, II, 1271) gives m. p. 223° for the acid prepared by direct bromination of *p*-toluic acid. The acid (12·5 g.) was dissolved in concentrated ammonia (200 ml.) and after 48 hours the solution was concentrated under reduced pressure and the product precipitated with acetic acid. After four recrystallisations from water (30 parts), *p*-aminomethylbenzoic acid was obtained as flattened tetrahedra, m. p. 343° (Found: N, 9·20. Calc. for $C_8H_9O_2N$: N, 9·27%).

Di-(p-aminomethylphenyl) Sulphone, $(NH_2 \cdot CH_2 \cdot C_6H_4)_2SO_2$.—(*a*) A suspension of di-(*p*-aminophenyl) sulphone (30 g.) in water (150 ml.) and concentrated hydrochloric acid (100 ml.) was diazotised at 0° with sodium nitrite (17 g.) in water (41 ml.) and added to a solution of sodium cyanide (58 g.) and nickel chloride hexahydrate (56 g.) in water (370 ml.) at 90°. The precipitated solid was collected and extracted with acetone. On evaporation to about 200 ml., di-(*p*-cyanophenyl) sulphone separated as a cream coloured crystalline powder, m. p. 237° after recrystallisation from acetone (Found: N, 10·05; S, 11·8. Calc. for $C_{14}H_8O_2N_2S$: N, 10·45; S, 12·0%). A suspension of the cyanide (1 g.) in alcohol (50 ml.) and concentrated hydrochloric acid (10 ml.) was hydrogenated at 21°/1205 mm. in the presence of palladised charcoal (2 g.) (total absorption, 220 ml. Calc., 225 ml.). After removal of the catalyst and concentration of the filtrate, *di-(p-aminomethylphenyl) sulphone dihydrochloride* was obtained as white needles, sparingly soluble in water, having m. p. *ca.* 340° (decomp.) (Found: N, 7·8; S, 9·6; Cl, 20·0. $C_{14}H_{16}O_2N_2S$,2HCl requires N, 8·0; S, 9·2; Cl, 20·3%).

(*b*) This method is based on that of Delépine (*Compt. rend.*, 1897, **124**, 292). A solution of di-(*p*-bromomethylphenyl) sulphone (15 g.) in chloroform (30 ml.) was added to a warm solution of hexamine (11 g.) in chloroform (140 ml.). The addition compound began to separate rapidly and after 30 minutes' refluxing it was obtained quantitatively as white crystals, m. p. 142°. This material (10 g.) was refluxed with alcohol (20 ml.) and concentrated hydrochloric acid (10 ml.). At first a clear solution was formed, but crystallisation rapidly took place. After 30 minutes' boiling the alcoholic hydrochloric acid was evaporated and the process was repeated three times. After recrystallisation from water the product was identical with that obtained by method (*a*).

By the addition of sodium hydroxide solution to a warm concentrated aqueous solution of the salt, *di-(p-aminomethylphenyl) sulphone*, was precipitated as an oil which rapidly hardened. After thrice recrystallising it from water (30 parts) it was obtained as white needles, m. p. 114° (Found: N, 9·9; S, 11·5. $C_{14}H_{16}O_2N_2S$ requires N, 10·1; S, 11·6%).

p-Chlorobenzylamine, $C_6H_4Cl \cdot CH_2 \cdot NH_2$.—This compound has been prepared by the action of alcoholic ammonia on *p*-chlorobenzyl chloride (Berlin, *Annalen*, 1869, **151**, 137; Jackson and Field, *Amer. Chem. J.*, 1880, **2**, 92) together with the corresponding secondary and tertiary amines and by hydrolysis of *NN'*-di-(*p*-chlorobenzyl)urea (Curtius, *J. pr. Chem.*, 1914, **89**, 533). These methods are tedious, and the following simple procedure gave good results. By the Sandmeyer method *p*-chloroaniline was converted into *p*-chlorophenyl cyanide which was isolated by steam distillation and was obtained after recrystallisation from alcohol (2 parts) as white crystals, m. p. 95°. The cyanide (5 g.) was dissolved in alcohol (50 ml.) and concentrated hydrochloric acid (6 ml.), and hydrogenated in the presence of palladised charcoal (5 g.) at 20°/1369 mm. (absorption, 880 ml. Calc., 920 ml.). After dilution with water (100 ml.) and filtration the solution was concentrated until the hydrochloride crystallised. It was obtained as flat white needles, m. p. 254° (Jackson and Field found m. p. 239—241°, Curtius, 250°). Treatment of an aqueous solution of the salt with excess of sodium hydroxide followed by extraction with ether gave the corresponding base, and this, by treatment with acetic anhydride, gave *p*-chlorobenzylacetamide, m. p. 109° after recrystallisation from alcohol (2 parts).

p-Acetamidomethylbenzenesulphinic Acid, $NHAc \cdot CH_2 \cdot C_6H_4 \cdot SO_2H$.—This was satisfactorily prepared by the method described for *p*-acetamidobenzenesulphinic acid (Bere and Smiles, *J.*, 1924, 2361). Damp *p*-acetamidomethylbenzenesulphonyl chloride (300 g. = 150 g. approx. of dry material) was added to a solution of anhydrous sodium sulphite (300 g.) in water (900 ml.) in three portions, 40% sodium hydroxide solution (total of 170 ml.) being added so as to keep the mixture just alkaline. When solution was complete the crude acid was precipitated with 60% sulphuric acid (200 ml.); after recrystallisation from water (500 ml.) and drying in a vacuum the *compound* was obtained as irregular plates, m. p. 148° (Found: N, 6·8; S, 15·2. $C_9H_{11}O_3NS$ requires N, 6·6; S, 15·0%).

p-Aminophenyl p-Aminomethylphenyl Sulphone, $NH_2 \cdot CH_2 \cdot C_6H_4 \cdot SO_2 \cdot C_6H_4 \cdot NH_2$.—Attempts to prepare *p*-acetamidophenyl *p*-cyanophenyl sulphone and *p*-nitrophenyl *p*-cyanophenyl sulphone from the corresponding amines were unsuccessful as also were attempts to condense *p*-chlorobenzylamine or *p*-chlorobenzylacetamide with sodium *p*-acetamidobenzenesulphinate. The following method gave good results. To a solution of *p*-acetamidomethylbenzenesulphinic acid (10 g.) and sodium carbonate (2·5 g.) in warm ethylene glycol (100 ml.) was added *p*-chloronitrobenzene (7·4 g.) and the mixture was refluxed for six hours. On cooling, crude *p-nitrophenyl p-acetamidomethylphenyl sulphone* separated (5·3 g.); after recrystallising from alcohol (150 ml.) it was obtained as pale cream coloured needles, m. p. 214° (Found: N, 8·6; S, 9·25. $C_{15}H_{14}O_5N_2S$ requires N, 8·3; S, 9·5%). This substance (2·5 g.) was suspended in concentrated hydrochloric acid (50 ml.) and water (30 ml.) and boiled for one hour. The solid rapidly dissolved and then the sparingly soluble *p*-nitrophenyl *p*-aminomethylphenyl sulphone hydrochloride began to separate. On cooling a total yield of 2·4 g., m. p. 256°, was obtained. This material (2·3 g.) was suspended in 10% hydrochloric acid (30 ml.) and hydrogenated in the presence of palladised charcoal (2·0 g.) at 20° and 1388 mm. (total absorption, 305 ml. Calc., 274 ml.). The sparingly soluble product which separated during the reaction was dissolved by heating, and the catalyst was filtered off. On cooling, *p-aminophenyl p-aminomethylphenyl sulphone dihydrochloride* was obtained, m. p. 285° (Found: N, 8·7; S, 9·4; Cl, 21·4. $C_{13}H_{14}O_2N_2S$,2HCl requires N, 8·4; S, 9·6; Cl, 21·7%). The last two steps can be reversed; *i.e.*, reduction can precede hydrolysis. By adding sodium hydroxide to a concentrated aqueous solution of the dihydrochloride and recrystallising the precipitate from water (50 parts) *p-aminophenyl p-aminomethylphenyl sulphone* was obtained as white needles, m. p. 159° (Found: N, 10·6; S, 11·9. $C_{13}H_{14}O_2N_2S$ requires N, 10·7; S, 12·2%).

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91. *Physical and Chemical Properties of Organo-metallic Compounds. Part I. The Vapour Pressures and Freezing Points of Simple Metal Alkyls of Groups II, III, and V.*

By C. H. Bamford, D. L. Levi, and D. M. Newitt.

Measurements are recorded of the vapour pressures and freezing points of dimethyl-, diethyl-, di-*n*-propyl-, and di-*n*-butyl-zinc, trimethyl-, tri-*n*-propyl-, and tri*iso*propyl-boron, solutions of trimethylboron in *n*-heptane, trimethyl- and triethyl-aluminium, trimethyl- and triethyl-stibine, dimethylcadmium and trimethylbismuth. From the vapour-pressure curves, the boiling points, latent heats of vaporization, and the Trouton constants have been calculated.

The preparation in a pure state of those metal alkyls which are spontaneously oxidizable at room temperatures presents experimental difficulties which are reflected in the absence, or comparatively wide variations, of recorded values of their physical constants. For example, in the case of the zinc alkyls recorded values of the boiling points differ by 2° for the dimethyl, by 5° for the diethyl and by 14° for the *n*-propyl derivative. No data for the freezing points of boron, aluminium, antimony, cadmium, and bismuth alkyls are available and the vapour-pressure data are scanty or absent.

Fig. 1.

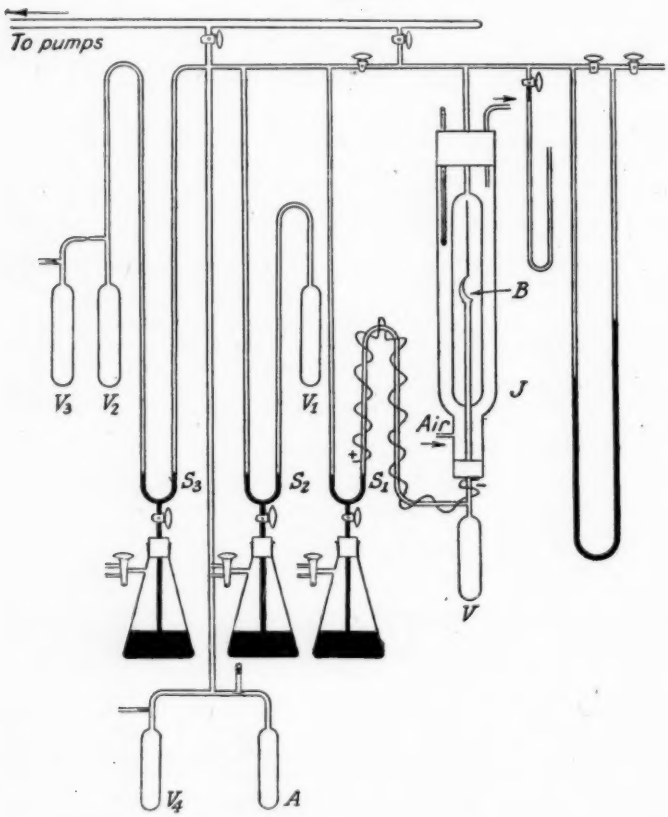
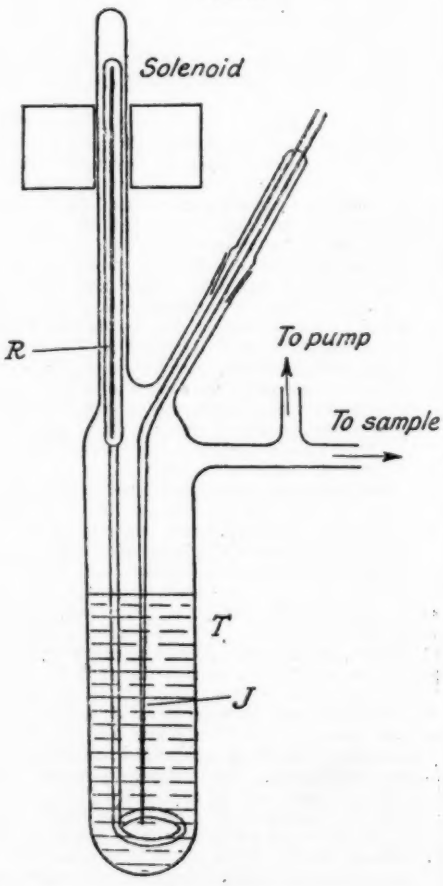


Fig. 2.



In the course of an investigation into the properties of a series of these compounds, described in subsequent papers, advantage has been taken of the availability of pure specimens to determine the vapour pressure–temperature curves, freezing points and, in some instances, the heats of combustion. The vapour-pressure and freezing-point data are included in the present paper.

Experimental.

Determination of Vapour Pressures.—The apparatus employed is shown in Fig. 1. Pressures are measured by a Bourdon gauge *B*, which is maintained at any desired temperature by the air-jacket *J*, and can be read to 0·01 mm.

The tube containing the sample is fitted with a vacuum breaker and is sealed on at A, and the whole evacuated. The breaker is then operated and about one-third of the liquid distilled into V_1, which is then isolated by raising the mercury in the U-tube S_2. The three mercury seals S_1, S_2, and S_3 are employed so that the vapours of the alkyls do not have to pass through taps before their pressures are measured. The middle third is distilled into V_2 and isolated, and the two end fractions united by distilling the liquids in V_1 and in the original container into V_4, which is then sealed off at a constriction. A portion of the middle fraction is taken to V and its vapour pressure determined at a suitable (low) temperature; S_1 is then lowered so that V is connected to the pump for a short time. The vapour pressure is then redetermined, and the process repeated until a consistent value is obtained. The whole vapour-pressure curve is then determined, for both rising and falling temperatures. The heating coil H enables measurements to be made above room temperatures. By adopting this procedure, any thermal decomposition of the alkyl is at once detected. The liquid in V is then pumped away. After distillation of a fraction of the liquid in V_2 to V_3, a further sample is taken to V, and another vapour-pressure curve obtained, to test the homogeneity of the middle fraction in V_2. If satisfactory agreement is obtained, the middle fraction is completely distilled into V_3, which is fitted with a vacuum breaker, and sealed off.

Determination of Freezing Points.—The apparatus employed is shown in Fig. 2. The alkyl is distilled under a vacuum into the tube T, which is then sealed. The cooling curve for the liquid is determined by immersing T in a suitable low-temperature bath and measuring temperatures by a copper–constantan thermocouple J sealed into the vessel. Stirring is effected by means of a totally enclosed magnetic stirrer R.

Results.—The vapour-pressure data are shown in Figs. 3 and 4 as plots of $\log_{10}p$ and the reciprocal of the absolute temperature. In general, the relationship is linear over the indicated temperature range, and the data may conveniently be summarised in the form of an equation $\log_{10}p = -A/T + B$. The boiling points (extrapolated) and latent heats of vaporization (L) are derived from the vapour-pressure data.

In most instances the alkyls gave sharply defined freezing points which could be estimated with an accuracy of $\pm 0{\cdot}15°$. An exception was di-*n*-propylzinc, which became very viscous in the neighbourhood of its freezing point and eventually solidified to a transparent glass. After standing for several hours the solid tended to crystallize.

The values of A and B in the above equation and the other physical constants are given in the accompanying table, L/T being Trouton's constant.

The Zinc Alkyls.—The data for the four zinc alkyls are shown in Fig. 3.

Alkyl.	Values in v.-p. formula. A.	B.	B. p./760 mm.	L, cals./mol.	L/T.	F. p.
$ZnMe_2$ [1]	1560	7·802	44°	7,150	22·5	− 29·2°
$ZnEt_2$ [2]	2109	8·280	117·6	9,605	24·6	− 30·0
$ZnPr^{\alpha}_2$	2099	7·969	139·4	9,620	23·3	−81 to −84
$ZnBu^{\alpha}_2$	2241	7·608	201·1	10,260	21·7	− 57·7
BMe_3 [3]	1250 *	7·906 *	−21·8	5,721	22·8	−153
BPr^{α}_3	2085	7·662	164·5	9,550	21·8	− 65·5
BPr^{β}_3	2091	7·862	147·4	9,570	22·8	− 52·5
$AlMe_3$ [4]	2148 †	8·279 †	125·3	9,830	24·7	15·0
$AlEt_3$ [5]	2826	8·778	207·0	12,930	26·9	—
$SbMe_3$	1627	7·496	80·6	7,450	21·1	− 62·0
$SbEt_3$	2183	7·904	161·4	9,993	23·0	− 98·0
$CdMe_2$	1850	7·764	105·7	8,468	22·3	− 4·2
$BiMe_3$	1815	7·659	107·1	8,308	21·8	− 85·8

* Up to 450 mm. † Over the temperature range 17—100°.

[1] I.C.T. give b. p. 45—47°, f. p. −40°. Thompson and Linnett (*Trans. Faraday Soc.*, 1936, **36**, 681) give b. p. 46·9°, L 6840.

[2] I.C.T. give b. p. 118°, f. p. −28°, −22°. Thompson and Linnett (*loc. cit.*) give b. p. 123°, L 8780.

[3] Stock and Zeidler (*loc. cit.*) give b. p. −20·2°/760 mm.

[4] Laubengayer and Gilliam (*loc. cit.*) give $A = 2104$, $B = 8{\cdot}125$ (temp. range, −23° to −70°); b. p. 126·1°; L 9600; L/T 24·1.

[5] Laubengayer and Gilliam (*loc. cit.*) give $A = 3625$, $B = 10{\cdot}784$ (temp. range, 110—140°); b. p. 185·6°; L 16,660; L/T 36·2.

Dimethylzinc. Vapour pressures were determined over the temperature range −25° to +45°, corresponding to a pressure range 30—770 mm. of mercury. The $\log_{10}p$–$1/T$ plot is linear over practically the whole range, with a slight but perceptible falling off in the region of highest pressure. The data were readily reproducible in different determinations, and also for rising and falling temperatures.

Di-n-propylzinc. Above about 70° thermal decomposition of the alkyl becomes perceptible, and at 100° it can be followed on the Bourdon gauge.

Di-n-butylzinc. Vapour pressures were determined up to 120° (75 mm.), no decomposition being detectable even at the highest temperature.

Boron Alkyls.—The vapour-pressure data for three alkyls are shown in Fig. 4.

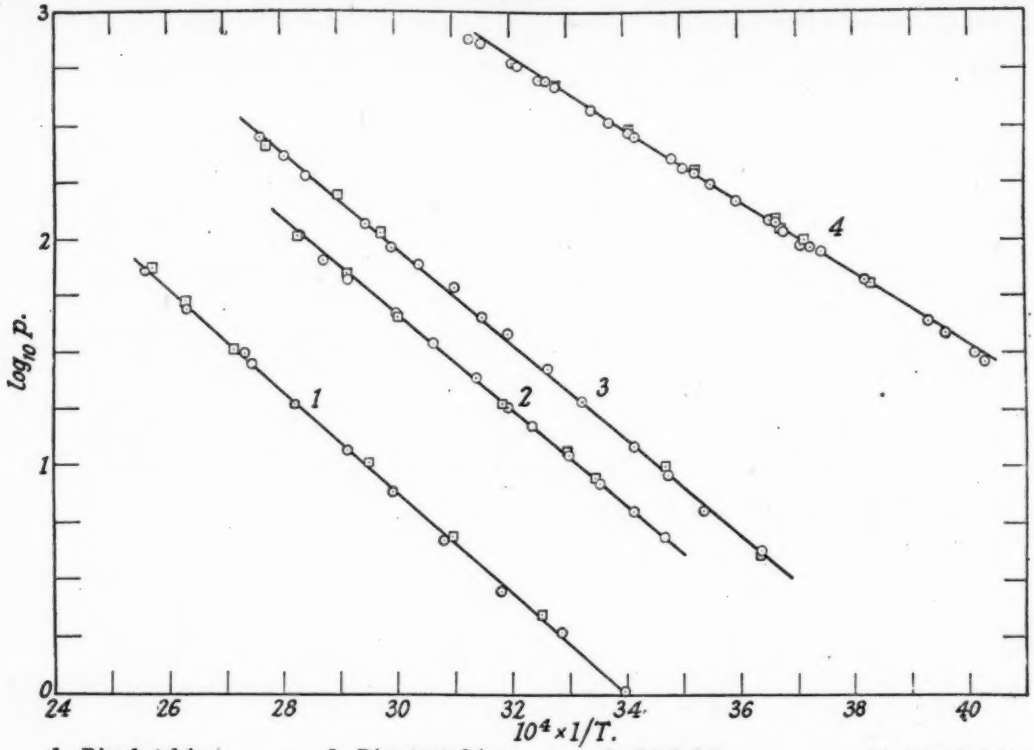
Trimethylboron. Six separate determinations of the vapour-pressure curve were made, but although agreement between them was fairly good, it was less so than with the other alkyls studied. Variations were almost certainly due to small traces of dissolved gas remaining in the liquid at the low temperatures used (−90° to −20°). The $\log_{10}p$–$1/T$ plot is linear only up to about 450 mm., above which the measured pressures are lower than would correspond with a linear relationship. The data of Stock and Zeidler (*Ber.*, 1921, **54**, 531) agree with the present results up to about 350 mm. but deviate more from linearity at higher pressures.

Tri-n-propylboron. Vapour pressures were determined over the range 0—120°, the highest pressures being about 200 mm. Pressure values determined during cooling were always slightly higher than those obtained with rising temperatures, possibly owing to traces of dissolved gas.

Triisopropylboron. After careful fractionation in a vacuum to remove ether and dissolved gases, the compound gave reproducible vapour pressures inthe range 0—120°, there being no indication of thermal decomposition.

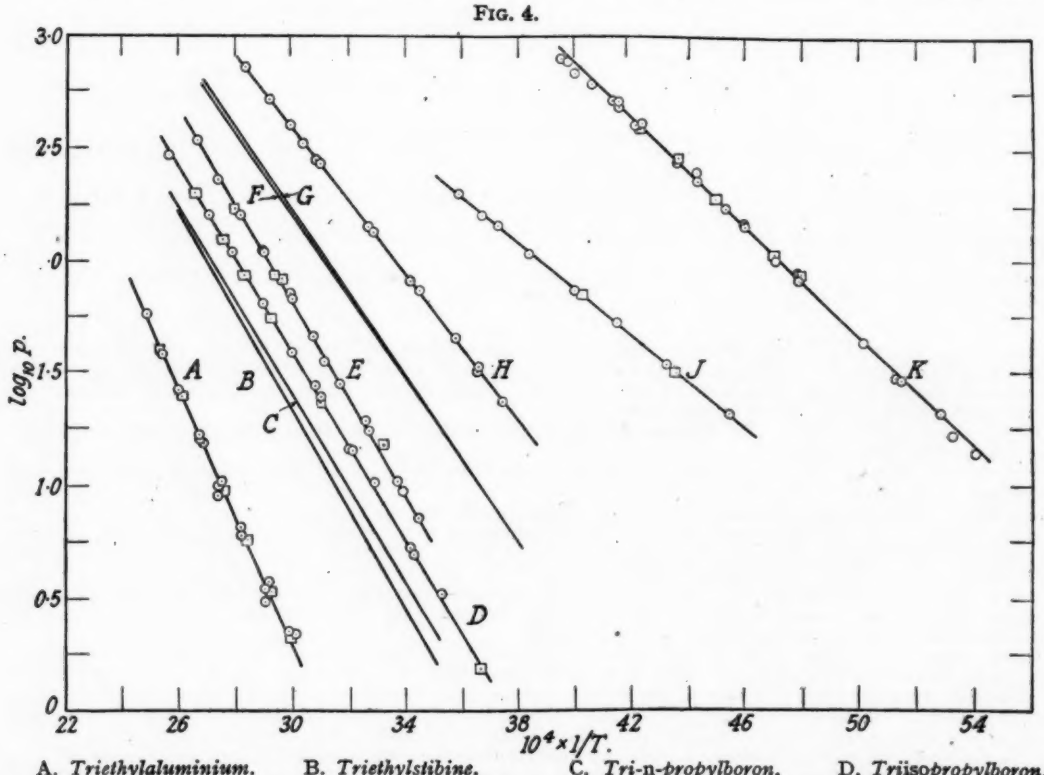
Solutions of trimethylboron in n-heptane. The experimental procedure was to condense separately measured quantities of the solvent and the alkyl vapours, warm them slowly to 0° and allow them to mix. The approach to equilibrium, which required several hours for completion, was accompanied by a steady decrease in pressure. Measurements of

FIG. 3.



1. *Di*-n-*butylzinc.* 2. *Di*-n-*propylzinc.* 3. *Diethylzinc.* 4. *Dimethylzinc.*

FIG. 4.



A. *Triethylaluminium.* B. *Triethylstibine.* C. *Tri*-n-*propylboron.* D. *Tri*iso*propylboron.*
E. *Trimethylaluminium.* F. *Dimethylcadmium.* G. *Trimethylbismuth.* H. *Trimethylstibine.*
J. 5·64% *soln.* $B(CH_3)_3$ *in* n-*heptane.* K. *Trimethylboron.*

the vapour pressure were made with falling and with rising temperatures, corrections being applied for the changes in composition of the two phases with temperature. The following solutions were used :

(1) 5·64 G. of BMe_3 per 100 g. of solution (Mol.-fractn. of BMe_3 = 0·096)
(2) 10·43 G. „ „ „ („ „ „ = 0·180)
(3) 14·33 G. „ „ „ („ „ „ = 0·230)

The log $_{10}p$–$1/T$ plots for the three solutions are given in Fig. 4. The vapour pressures are about 20% higher than would be predicted from Raoult's law and, in consequence, the latent heats are lower than that of the pure alkyl.

The data are summarised below :

% Alkyl in solution.	Vapour pressure.	Partial pressure at 20°, mm.	L, cals./mol.
5·64	$\log_{10} p = -1033/T + 5·996$	302	4730
10·43	$\log_{10} p = -1004/T + 6·214$	603	4593
14·33	$\log_{10} p = -1093/T + 6·592$	832	5005

The Aluminium Alkyls.—The vapour-pressure data are shown in Fig. 4.

Trimethylaluminium. Vapour pressures were measured up to 100° without any sign of decomposition, the results being satisfactorily reproducible. This substance is, however, associated in the vapour state and there is a progressive decrease in its apparent molecular weight over the temperature range employed. Laubengayer and Gilliam (*J. Amer. Chem. Soc.*, 1941, **63**, 477) have shown that the molecular weight in the neighbourhood of 70° corresponds to that of the dimer.

The difference in the two vapour-pressure equations is in large part attributable to the different ranges of temperature employed and the occurrence of dissociation.

Triethylaluminium. This compound has a low volatility and distils extremely slowly in a vacuum. It was, therefore, necessary to make the pressure measurements directly with a mercury manometer. After prolonged pumping to remove dissolved gases, measurements were made in the range 40—125° (pressures up to 58 mm.).

According to Laubengayer and Gilliam triethyaluminium is about 12% associated to the dimer at 150·6°; they also note that, when heated above 165°, it undergoes a decomposition which involves a decrease of the number of molecules in the vapour state. They point out that their value for the heat of vaporization is probably too high because it includes some heat of dissociation.

The Antimony Alkyls.—Trimethylstibine. The pure liquid gave closely reproducible pressures on heating and cooling.

Triethylstibine. Pressures were measured over the range 0—120° without any evidence of decomposition.

The determination of the data for the cadmium and the bismuth alkyls does not require any special comment.

Preparation and Purification of Alkyls.—Dimethylzinc. The method described by Greenlaw and Renshaw (*J. Amer. Chem. Soc.*, 1920, **42**, 1472), in which the appropriate alkyl iodide is heated with a zinc–copper couple, was employed. 36 G. of methyl iodide, with 110 g. of the couple and 2 drops of ethyl acetate, afforded a 90% yield of crude substance.

Diethylzinc. By the above procedure 65 g. of ethyl iodide and 165 g. of zinc–copper couple gave a 95% yield of crude diethylzinc.

Di-n-propylzinc. The method described by Noller (*J. Amer. Chem. Soc.*, 1929, **51**, 594), in which a couple containing 5—8% of copper is heated with equimolecular quantities of alkyl iodide and bromide, was employed, 85 g. of the iodide and 61·5 g. of the bromide (with 130 g. of the couple) giving an 85% crude yield.

Di-n-butylzinc. This was prepared from *n*-butyl iodide by the above method.

Purification of the zinc alkyls. The crude product contains alkyl iodide (and bromide), which can best be removed by two or three passages over a zinc–copper couple heated electrically to about 150°. Any hydrocarbon impurity arising from the decomposition of the alkyl can be removed by distillation under reduced pressure. The absence of alkyl iodide in the purified product was confirmed by the absorption spectrum.

Trimethyl-, triethyl-, tri-n-propyl-, and triisopropyl-boron. By passing dry boron trifluoride into the appropriate Grignard reagent yields representing about 50% of the theoretical were obtained.

Trimethylaluminium. By heating dimethylmercury (124 g.) with excess of aluminium powder (15 g.) in a sealed tube at 100° for 24 hours and fractionating the product in a vacuum, a nearly theoretical yield was obtained.

Triethylaluminium. Similarly, diethylmercury (20 g.) and aluminium (6 g.) gave an almost theoretical yield.

Trimethylstibine. This was prepared by the action of antimony trichloride on the Grignard reagent. A satisfactory separation of the alkyl from ether could not be obtained by fractionation in a vacuum, so the product was isolated *via* the dibromide, $SbMe_3Br_2$. This was prepared by running bromine into the ethereal solution of trimethylstibine until the liquid was just coloured. The dibromide was filtered off, washed with alcohol and ether, and dried (yield *ca.* 65%); it was decomposed by heating to 150° under reduced pressure with an excess of finely granulated zinc and a few c.c. of water. The product, consisting of trimethylstibine and a little water, was dried over calcium chloride and purified by fractionation in a vacuum. Materials : methyl iodide, 142 g.; magnesium, 24 g.; absolute ether, 800 c.c.; antimony trichloride, 74 g. in 300 c.c. of ether. Yield, 45%.

Triethylstibine. This was prepared by the action of antimony trichloride (74 g. in 300 c.c. of ether) on the Grignard reagent (Mg, 24 g.; EtI, 156 g.; ether, 800 c.c.). The bulk of the ether was distilled off under reduced pressure, and pure triethylstibine obtained by fractionation of the product in a vacuum. Purification by means of the dibromide was not necessary. Yield 60%.

Dimethylcadmium. This was similarly prepared ($CdBr_2$, 100 g. in 200 c.c. of ether; MeI, 142 g.; Mg, 24 g.; ether, 400 c.c.). The ether was separated by repeated fractionation under reduced pressure and in a vacuum. Yield 80%.

Trimethylbismuth. By the same procedure as in the preceding case ($BiCl_3$, 76 g. in 300 c.c. of ether; MeI, 107 g.; Mg, 18 g.; ether, 500 c.c.), a 40% yield was obtained.

We wish to thank Miss B. M. Gaunt, B.Sc., for valuable assistance in preparing the pure samples of alkyls used in this work.

[*Received, November 26th*, 1945.]

92. *Cinnolines. Part V. The Reaction between Pyridine, Acetic Anhydride, and 4-Hydroxycinnoline-3-carboxylic Acid.*

By K. Schofield and J. C. E. Simpson.

Treatment of 4-hydroxycinnoline-3-carboxylic acid (I) with a mixture of pyridine and acetic anhydride under appropriate conditions produces a *substance*, $C_{16}H_{11}O_3N_3$, believed to be a resonance hybrid of the species (II, *a*—*c*) with the carbonium form (II*a*) making a major contribution. In its formulation, the production of "Reissert" compounds from quinoline, acid chlorides, and potassium cyanide has been used as a model, and ample experimental evidence is put forward in support for this analogy. Various reactions are described in which this substance, and its addition products (III, IV) with aniline and alcohols, are involved. Stepwise degradation of it has led to the isolation of derivatives of a new ring-system, provisionally represented as 3 : 9 : 10-*triazaphenanthrene* (as XIII), and also to the production of 4-(2′-*pyridyl*)*cinnoline* (X).

Comparative experiments have shown that the reaction with pyridine and acetic anhydride is highly specific to 4-hydroxycinnoline-3-carboxylic acids, as the 6-methoxy-acid undergoes a precisely similar reaction, but no comparable reaction occurs with the analogous quinolinecarboxylic acid or with 2-hydroxy-3-naphthoic acid.

In a previous paper (Schofield and Simpson, *J.*, 1945, 512) we stated that a complex reaction occurs when the three substances named in the title are heated together. Further study showed that the presence of both reagents is necessary—4-hydroxycinnoline-3-carboxylic acid (I) gives 4-acetoxycinnoline when boiled with acetic anhydride alone (Schofield and Simpson, *loc. cit.*), and the acid crystallises unchanged from pyridine—and that the reaction is specific to the particular grouping represented by the heterocyclic ring of (I). Thus 4-hydroxycinnoline gives 4-acetoxycinnoline when heated with acetic anhydride either alone or in pyridine solution (*loc. cit.*), and ethyl 4-hydroxycinnoline-3-carboxylate (unpublished) behaves similarly; we have also found that the mixed reagents convert 2-hydroxy-3-naphthoic acid into the normal acetoxy-acid, and are without action on 4-hydroxyquinoline-3-carboxylic acid. On the other hand, similar treatment of 4-hydroxy-6-methoxycinnoline-3-carboxylic acid brings about a complex reaction which is apparently exactly analogous to that which occurs with the Richter acid (I). In view of the highly specific nature of the reaction which these comparative experiments establish, and also because of the great reactivity of the product derived from (I), we now record an account of partly completed experiments in this field, which we hope to extend in various directions as opportunity allows.

When the Richter acid, pyridine, and acetic anhydride were heated at 60° and at 95° in the proportions of 2 : 9 : 13 approximately, a *substance*, m. p. 217°, gradually separated. This showed clearly defined amphoteric properties in the cold, but was decomposed by hot acid and alkali, and also by boiling solvents such as pyridine and the lower alcohols. This extreme reactivity, coupled with solubility characteristics, made it somewhat uncertain whether complete reliance could be placed on analytical data, but the mean value of analyses on three samples indicated that the most probable formula was $C_{16}H_{11}O_3N_3$ or $C_{21}H_{16}O_4N_4$.

The substance dissolved slowly in boiling methanol, ethanol, and *iso*propanol to form strongly fluorescent solutions, and on concentration of these solutions a series of *substances* resulted which, like their common precursor, were ampholytes and unstable to hot acid and alkali. Analyses showed that they were homologues derived from the parent substance by addition of the alcohols in question.

A study of the analytical data for the four substances showed that they could be represented by either of two series of formulæ, *A* and *B* (see table below).

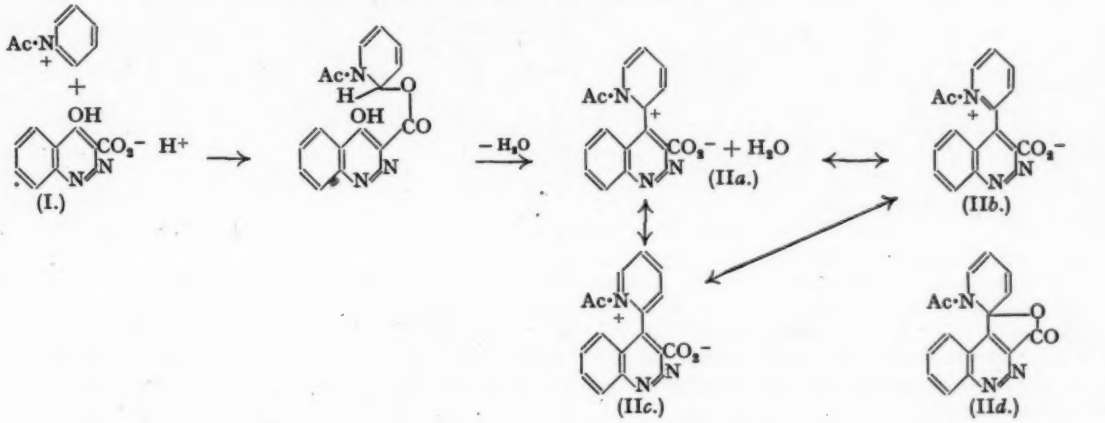
	Series A.	Series B.
Primary reaction product, m. p. 217°	$C_{16}H_{11}O_3N_3$	$C_{21}H_{16}O_4N_4$
Product from methanol	$C_{17}H_{13}O_4N_3$	$C_{22}H_{20}O_5N_4$
Product from ethanol	$C_{18}H_{17}O_4N_3$	$C_{23}H_{22}O_5N_4$
Product from *iso*propanol	$C_{19}H_{19}O_4N_3$	$C_{24}H_{24}O_5N_4$

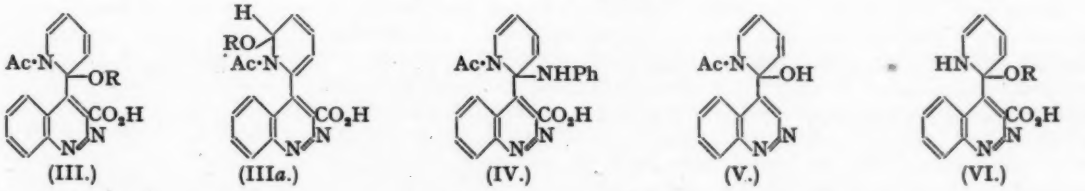
On the basis of nitrogen content, Series *A* would imply that the substance, m. p. 217°, is formed by condensation of a cinnolyl and a pyridyl residue; if, on the other hand, the sequence of products were correctly represented by Series *B*, then the primary reaction would involve condensation between a cinnolyl and two pyridyl groups, or, alternatively, a fusion of two cinnoline molecules, which would thus be stoicheiometrically independent of the basic solvent (*i.e.*, pyridine). In order to decide between these possibilities, the pyridine was replaced by quinoline; reaction again occurred, and although the primary product was not purified, reaction with ethanol furnished a *substance*, m. p. 170°, which differed from the corresponding compound, m. p. 128°, obtained from the pyridine reaction, and, as the analysis of the quinoline derivative was in much better agreement with Series *A* than with Series *B*, it followed that the original (pyridine) reaction could be represented as:

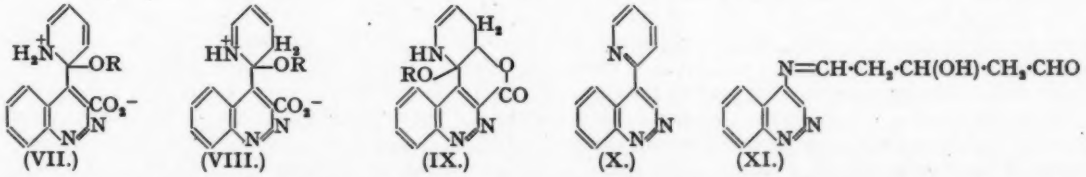
$$C_9H_8O_3N_2 + C_5H_5N + (CH_3{\cdot}CO)_2O \longrightarrow C_{16}H_{11}O_3N_3 + CH_3{\cdot}CO_2H + H_2O.$$

Further variations were then tried. The substitution of quinaldine for quinoline led to recovery of the Richter acid in high yield and caused no development of colour or fluorescence; α-picoline showed evidence (colour-development) of reaction, possibly due to impurity, as the only isolable product was unchanged Richter acid; and propionic anhydride with pyridine gave an obvious reaction, but the product was an oil. The quinoline ethanolysis product referred to above was obtained on only one occasion, several attempted repetitions giving only uncrystallisable oils, but the analyses of the numerous derivatives described later leave no doubt that Series *A*, and not Series *B*, is the correct one.

In seeking a possible explanation of these facts, our attention became focused on two alternative lines of approach to known analogies, namely the tendency of the quinolinium kation to assume covalency with a weak anion (*i.e.*, the formation of *N*-substituted 1 : 2-dihydroquinolines), and the ease with which fission of the pyridine ring may occur in certain circumstances, producing derivatives of glutacondialdehyde. In illustration of the first reaction, many examples of the formation of (covalent) pseudo-bases from quinolinium and pyridinium hydroxides have been observed (*e.g.*, Decker, *Ber.*, 1892, **25**, 443; Hantzsch and Kalb, *ibid.*, 1899, **32**, 3119), and Reissert (*ibid.*, 1905, **38**, 1603) has shown that quinoline, benzoyl chloride, and alkali cyanide yield *N*-benzoyl-2-cyano-1 : 2-dihydroquinoline, which in presence of acid furnishes quinaldinic acid, *via* the nitrile, by loss of benzaldehyde (see also Woodward, *J. Amer. Chem. Soc.*, 1940, **62**, 162; Grosheintz and Fischer, *ibid.*, 1941, **63**, 2021; Buchanan, Cook, and Loudon, *J.*, 1944, 325). If, then, in the condensation between the Richter acid (I), pyridine, and acetic anhydride, the first were to function as a weak anion, the reaction could take the course [(I) ⟶ (II, *a*—*c*)].







Formal representation of the substance $C_{16}H_{11}O_3N_3$, m. p. 217°, by any of the three unperturbed structures (II, *a*—*c*) is to be preferred to the lactone form (II*d*) for the following reasons. First, its physical properties suggest a polar structure. Secondly, it is readily soluble in cold aqueous sodium carbonate. Thirdly, the facile additions of alcohols to give (III; R = Me, Et, and Pr^{β}) are more readily understood on the basis of ionic attack on a zwitterion than by the assumption that lower alcohols at their boiling points could bring about hydrolysis of the structure (II*d*). Such ionic attack could take place in either of two ways—by electromeric shift in the resonance hybrid towards the extreme form (II*b*), leading, *via* the usual quaternary salt–pseudo-base mechanism, to entry of the OR anion and formation of the pseudo-base ether, or, more simply and probably, by direct attack of OR on the carbonium ion (II*a*). Statistically, therefore, this homologous series of ether-acids is more likely to have the constitution (III) than (III*a*), which could only emerge from the species (II*c*). In complete agreement with the production of these ether-acids is the observation that the substance $C_{16}H_{11}O_3N_3$ adds on a molecular proportion of aniline in boiling benzene solution, yielding an *acid* (IV).

The fourth reason for preferring the dipolar structure (II, *a*—*c*) to the lactone form (II*d*) is that the compound $C_{16}H_{11}O_3N_3$ undergoes extremely facile hydration-decarboxylation, under certain conditions, to a colourless *base*, $C_{15}H_{13}O_2N_3$. This base was produced in comparatively high yield (a) when the zwitterion compound was refluxed in ordinary " purified " pyridine, and (b) * when a mixture of 4-hydroxycinnoline-3-

* This was the method selected for routine preparation of the base, $C_{15}H_{13}O_2N_3$. Under these conditions, a small yield (2—3%) of a second crystalline *substance* of formula $C_8H_{6(7)}O_5N$ was produced. This substance was unchanged by short boiling with aqueous sodium hydroxide—a fact which differentiates it sharply from the substances under discussion—and has not been further investigated.

carboxylic acid, pyridine, and acetic anhydride, in the proportions of **1 : 3 : 1**, was refluxed for 30 minutes, none of the intermediate zwitterion being isolated under these conditions. In sharp contrast to this, no crystalline product was produced either when (c) a mixture of the Richter acid, pyridine, and acetic anhydride was refluxed in those proportions (**2 : 9 : 13**) which furnish the C_{16} zwitterion at reaction temperatures of 60° or 95°, or when (d) the C_{16} zwitterion was substituted for the Richter acid in experiment (c). Further observations were (e) that the base, $C_{15}H_{13}O_2N_3$, was unaffected by acetic anhydride at 95°, and (f) that the zwitterion gave a moderate yield of the above-mentioned base when its aqueous suspension was refluxed for several hours.

These facts cannot be satisfactorily interpreted on the basis of the lactone structure (II*d*), and our explanation, on present evidence, is that the C_{15} base has the constitution (V) and is derived from an intermediate hydroxy-acid (III; R = H) which cannot be isolated under the conditions used in our experiments. We consider that the initial step in the formation of (III; R = H) is a rapid attack of hydroxyl ion on (II*a*); this particular canonical state would be expected to show the greatest kationic activity of the three forms (II, *a*—*c*), and may well contribute significantly to the resonance hybrid. In the presence of acetic anhydride, however, the C_{16} zwitterion would be forced to compete for any available hydroxyl ions, and this competition explains satisfactorily the high yield of (V) obtained both in experiment (a) [having regard to the fact that the pyridine used was not anhydrous and was present in considerable excess (**15 : 1**)] and in experiment (b) (where the proportion of acetic anhydride was low and a molecular proportion of water was eliminated during the first stage of the reaction). Again, the failure to isolate the base (V) from experiments (c) and (d) is in accord with the concept of competition, as in both these experiments the acetic anhydride was present in considerably greater quantity. The relatively poor yield of base from experiment (f) may be explained by the fact that the reaction was carried out on a suspension of the zwitterion in a neutral medium—conditions which would scarcely be expected to favour the postulated mechanism.

Our formulation of the series (II—V) as α-pyridinium (or α-dihydropyridyl) derivatives is based partly on the inhibition of reaction caused by substitution of quinaldine for pyridine or quinoline, and partly on analogy with the " Reissert compounds " (see above). This analogy, if well founded, should be susceptible of further substantiation by reactions involving the loss of the *N*-acetyl group of (III—V) (as acetic acid or its esters or anilide), and the following observations show that this adumbration is, indeed, largely borne out by experiment.

Treatment of (III; R = Me) with methanol–sulphuric acid yielded a bright yellow *substance*, which was also produced when ethanol was used instead of methanol. The reaction, therefore, cannot be one of esterification, and analytical data suggested that the most probable formula for the product is $C_{15}H_{13}O_3N_3$. Similar treatment of (III; R = Et) with both alcohols furnished identical specimens of a second *substance*, $C_{16}H_{15}O_3N_3$. The simplest explanation of these formulæ would be to regard the substances as secondary amines (VI; R = Me or Et) derived from (III; R = Me or Et) by deacetylation, the acetyl group concerned undergoing an amide–ester conversion. The two homologues, however, although showing the anticipated basic properties, were insoluble in cold aqueous sodium hydroxide. While it is true that insolubility in aqueous alkali is not invariably a criterion of the absence of a carboxyl group—for example, diphenyl-4-acrylic acid is almost insoluble in these reagents (Hey, *J.*, 1931, 2478)—there are obvious alternatives to (VI) which may be considered provisionally until further data are available. Thus * hydrogen bonding between the carboxyl and the >NH group of the dihydropyridine ring, or the transfer of a proton to the latter group, giving the dipolar structure (VII), might explain the properties of the two homologues. Other possibilities are (i) that the polarisability of the dihydropyridine ring (hetero-dienoid system) might be called into play, and the fully polarised form stabilised by a proton shift, giving (VIII), and (ii) that lactonisation between a double bond of the dihydropyridine ring and the carboxyl group could occur, producing (IX).

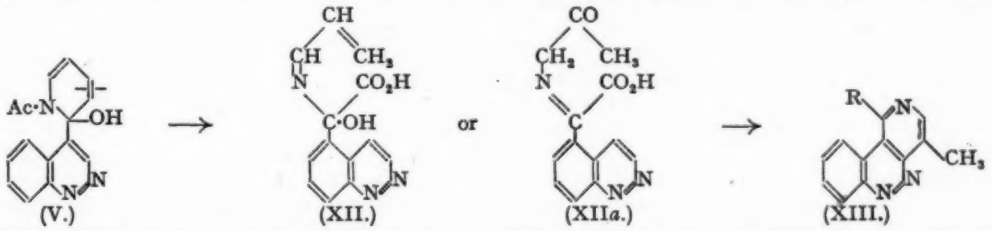
The action of hot aqueous sodium hydroxide on (VI; R = Me) led to further degradation with production of a *substance*, m. p. 153°, which showed basic, but no acidic, properties. This base is probably the end-product of mild acid or alkaline degradation of all members of the series (II—V); the decomposition of each member of the series has not yet been studied in detail, but, in addition to its formation from (VI; R = Me), the base has also been isolated by treatment of (V) with hot dilute hydrochloric acid or sodium hydroxide, by treatment of (III; R = Me) with either reagent, by the action of acid, followed by alkali, on (IV), and from the zwitterion (II) by means of hot acid. The compound (VI; R = Et), on the other hand, appeared to be stable under the roughly standard small-scale experimental conditions used; no attempt was made to recover it from the experiment, but no evidence could be observed of the production of the base, m. p. 153°, which in the other cases is formed in a highly characteristic manner involving, initially, the production of an intense permanganate-pink solution, the colour of which fades as the reaction proceeds.

On the basis of the constitutions which have been discussed, the only possible representation of the base, m. p. 153°, is the expression (X), and analytical data did, in fact, indicate a formula $C_{13}H_9N_3,2H_2O$. That the oxygen was present as water of crystallisation was eventually proved by analysis of the *picrate*, which

* For steric reasons, hydrogen bonding is not, as a rule, marked where the phenomenon would give rise to a seven-membered ring (cf. Remick, " Electronic Interpretations of Organic Chemistry," p. 42, Chapman & Hall, 1943), but one might anticipate a modified rôle for steric factors where the hydrogen and donor atoms are attached to different rings, as in (VI). A rough analogy is the production, so well known in bile acid chemistry, of anhydrides instead of ketones from substituted adipic acids in which one carboxyl group is attached to ring A and the other to ring C (or to B and D respectively) of the steroid nucleus.

was solvent-free; the *styphnate* was monohydrated, and the *hydrochloride* was a dihydrate. The base is rapidly oxidised by potassium permanganate at room temperature to an amphoteric compound, m. p. 146°, the structure of which is discussed below. In our view it was surprising that a substance of structure (X) should be so sensitive towards oxidation, and we should like to record that, at an early stage in our investigation, it was suggested to us by the research staff of Imperial Chemical Industries, Ltd., that the C_{13} base might be represented by some expression such as (XI), in order to account for the sensitivity which it displays towards permanganate. This hypothesis is based on analogies involving ring-opening of pyridine derivatives *via* intermediate quaternary salts (see, *e.g.*, Zincke *et al.*, *Annalen*, 1904, **330**, 361; **333**, 296; *J. pr. Chem.*, 1910, **82**, 1; Koenigs and Greiner, *Ber.*, 1931, **64**, 1049; Baumgarten, *ibid.*, 1926, **59**, 1166; 1933, **66**, 1633; 1936, **69**, 1938), and, although it was finally found to be untenable, it was of considerable value to us in furthering the progress of our work.

Of the various routes to the base (X) enumerated above, that involving the alkaline degradation of (V) was selected as being the most convenient for preparative purposes. The average yield from a number of experiments was only 60%, and an examination of the alkaline mother-liquors showed that the conversion of (V) to (X) is accompanied by side-reactions. Concentration of the alkaline filtrate readily yielded the sodium salt of a *substance*, m. p. 187°, of which the structure is discussed below. Acidification of the filtrate from this sodium salt furnished an *acid*, m. p. 170°, of formula $C_{13}H_9O_2N_3$, which also showed very slight basic properties. The acid underwent rapid and quantitative decarboxylation at the melting point, the product being a highly crystalline *substance*, m. p. 114°, of formula $C_{12}H_9N_3$, which showed definite, but rather weak, basic properties. On the basis of hydrogen content, this compound must contain a tricyclic skeleton in which all three nitrogen atoms participate. Now the production of the acid, $C_{13}H_9O_2N_3$, from the dihydropyridine base (V) must involve oxidative degradation in alkaline solution, and intermediate reactions, such



as hydration of the dihydropyridine ring, and disproportionation (probably *via* Cannizzaro reactions), must be reckoned with. The base $C_{12}H_9N_3$ could then be formulated as 1-*methyl*-3 : 9 : 10-*triazaphenanthrene* (XIII; R = H), and the acid $C_{13}H_9O_2N_3$ as the related 4-carboxylic acid (XIII; R = CO_2H), produced from (V) by cyclodehydration of the hypothetical intermediate (XII) or (XII*a*). The position of the carboxyl group in the acid is clearly one from which, by simple analogy, ready elimination would be anticipated.

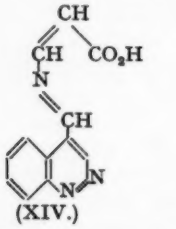
The substance, m. p. 187°, obtained from the sodium salt already mentioned, showed the behaviour of a weak ampholyte. Analytical data indicated the formula $C_{12}H_9ON_3$ or $C_{12}H_{10}ON_3$, and if the former be taken as correct the substance can be represented as (XIII; R = OH), an α-hydroxypyridine structure which is in accord with its weakly basic and weakly acidic properties.

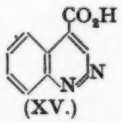
The conversion of (V) into (XIII; R = CO_2H or OH) represents a type of degradation that one would scarcely predict as characteristic of such a substance—in particular, ring-closure into a heterocyclic nucleus is not usually a facile process—and to that extent the structures (XIII; R = CO_2H, OH, and H) must be regarded as provisional, even though no open-chain constitutions appear to be possible. The structures advanced are obviously capable of some degree of confirmation by analytical study, and a possible synthetic proof, which it is hoped to test, would consist in the preparation of the appropriate heteronuclear dinitrophenylpyridine, followed by reduction, a method which is of general application in the preparation of 3 : 4-benzocinnolines (cf., *e.g.*, Ullmann and Dieterle, *Ber.*, 1904, **37**, 23).

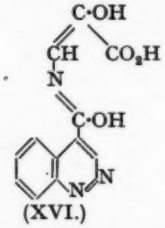
Acetic acid was identified in the filtrate from the acid (XIII; R = CO_2H), and, from the results of alkali titration, it was clear that the whole of the base (V) must have suffered loss of acetic acid during the polydirectional alkaline degradation; this is in conformity with the structures (X) and (XIII), and provides the final step in the analogy sought between the behaviour of (V) and the Reissert compounds.

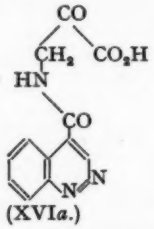
The oxidation product, m. p. 146°, is produced from the base (X) in comparatively high yield and is apparently unaccompanied by side-products. It is amphoteric, and, in contrast to the yellow base from which it is derived, is reddish-orange in colour. Qualitatively, the colours of its solutions in acid or alkali are also similar. Elementary analysis indicated the formula $C_{12}H_9O_2N_3$, confirmed by analysis of its crimson *picrate*. The solubility of the substance in aqueous bicarbonate suggests that it contains a carboxyl group rather than a phenolic or readily enolisable carbonyl group; if, therefore, as we believe, the base (X) is correctly formulated, the expression (XIV) appears to be the only representation of the oxidation product which accounts adequately for the solubility relationships and analytical data. The nitrogen-free analogue of (XIV), δ-(1-naphthyl)-pentadienoic acid, does not appear to have been prepared, but there is little doubt that the colour of such a substance would be very much lighter than that of (XIV)—for example, cinnamylideneacetic acid is colourless (Sudborough and Gittins, *J.*, 1909, **95**, 320), as also, apparently, is its *o*-nitro-derivative (although the

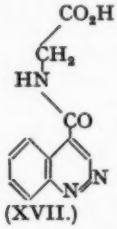
alkali-metal salts of this compound are bright yellow) (Diehl and Einhorn, *Ber.*, 1885, **18**, 2331), and α-phenyl-δ-(2-nitrophenyl)pentadienoic acid is yellow (Bachman and Hoaglin, *J. Org. Chem.*, 1943, **8**, 310). The deep colour of (XIV) must therefore be ascribed to the operation of pronounced bathochromic factors relative to its carbocyclic analogues, and these factors must clearly be bound up with the accumulation of nitrogen atoms in the extended conjugated system.* The bathochromic effect of a suitably located accumulation of nitrogen atoms has been clearly demonstrated for the quinoxaline cyanines in comparison with other cyanine types (Cook, Garner, and Perry, *J.*, 1942, 710; Cook and Perry, *ibid.*, 1943, 394; Anker and Cook, *ibid.*, 1944, 489), and we believe that the structure (XIV) accounts satisfactorily for the colour of the compound.


(XIV.)


(XV.)


(XVI.)


(XVI*a*.)


(XVII.)

The high resonance energy which, from the depth of colour, one would attribute to the substance, m. p. 146°, is in accord with what is known of its stability. Small-scale tests showed that it is stable towards cold or warm permanganate, although it seemed to be attacked to some extent by the reagent in boiling solution. [In contrast to this stability, cinnamylideneacetic acid, with, presumably, less resonance energy, is oxidised by cold permanganate to benzaldehyde and tartaric acid (Doebner, *Ber.*, 1890, **23**, 2372).] It was also found that the substance was not affected by boiling 10% aqueous sodium hydroxide (1½ hours), and 40% was recovered, as the sole crystalline product, after mild treatment with hydrochloric acid. Under more drastic conditions, however, it was converted by hydrochloric acid into a mixture of two products, neither of which was the anticipated unknown cinnoline-4-carboxylic acid (XV). One was a *substance*, m. p. 195°, whose properties closely resembled those of its precursor. It crystallised in orange-pink needles, was amphoteric, and appeared to be stable towards hot aqueous permanganate. The analytical data were in moderate agreement with the formulæ $C_{12}H_9O_4N_3$ and $C_8H_5O_3N_2$, and as the properties of the substance indicated that it is a near derivative of the compound formulated as (XIV), preference must be given to the C_{12} formula. On the basis of (XIV), the substance could then be represented as (XVI); the existence of the substance predominantly in the enolic, rather than in the ketonic, form (XVI*a*) must be assumed in order to account for the colour, and could well be due to the extra stability conferred on the enolic structure by reason of the extended conjugation.

The other component of the mixture formed by the action of hydrochloric acid on the acid (XIV) was a colourless *substance*, m. p. 254°. This, like the compound discussed above, showed amphoteric properties, but appeared to have much less avidity for both acids and bases. Analysis suggested the formula $C_{11}H_7O_3N_3$, but the agreement with theory was not close, and if, as seems probable, the compound was not obtained analytically pure, alternative formulæ $C_{12}H_9O_3N_3$ and $C_8H_6O_2N_2$ must also be reckoned with. Until further data are available, any formulation of the compound, m. p. 254°, must be based largely on speculation. However, it is clear that in its formation the conjugation characteristic of its concomitant, m. p. 195°, has been destroyed (significantly, the substance reduced aqueous permanganate), and it is suggestive that the molecular formula $C_{11}H_7O_3N_3$, with which the analytical data are in best agreement, is that of the expression (XVII), a simple analogue of (XVI*a*) in which ring–side-chain conjugation is no longer possible. [Enolisation of this, as compared with that of (XVI*a*), would probably be reduced, as it would not be stabilised by conjugation.]

The substance, m. p. 195°, is not, apparently, an intermediate in the formation of the compound, m. p. 254°; the former was to some extent attacked by hydrochloric acid under conditions which produced the mixture of the two substances from (XIV), but, on the scale employed, the only crystalline substance isolated was unchanged material in much diminished yield, and it was established that no appreciable quantity of the compound, m. p. 254°, was formed during the reaction.

The work described in this paper has had to be temporarily interrupted. It is hoped to resume it when an opportunity occurs, but until the substances, m. p. 195° and 254°, can be adequately characterised the structures discussed in relation to these compounds are regarded as purely tentative.

That the oxidation of (X) to (XIV) should occur so readily is unexpected, but, here again, we know of no comparable data on which analogies could be based. The closest analogues of (X) which appear in the literature are the 2- and 4-lutidylquinolines of Cook, Heilbron, and Steger (*J.*, 1943, 413), but no data on the oxidation of these substances are available. In any event, the present experiments amply demonstrate the lack of analogy in chemical behaviour between certain cinnoline derivatives and their quinoline analogues, and it is not difficult to imagine that the adjacent nitrogen atoms in the cinnoline nucleus of (X) may be

* On the other hand, Schwarzenbach, Lutz, and Felder (*Helv. Chim. Acta*, 1944, **27**, 584) state that the effect of the nitrogen atom in the anion of the substance OHC·[CH:CH]$_3$·N:CH·CH:CH·CH$_2$·CHO is hypsochromic. It is, however, to be noted that the absorption maximum of the nitrogen-free analogue, OHC·[CH:CH]$_4$·CH$_2$·CHO, required for comparison was obtained by extrapolation and not by experimental observation.

responsible for the setting up of considerable initial polarisation, resulting in a concentration of the attack of the oxidising agent solely on the pyridine ring.

Experimental.

(Melting points are uncorrected.)

Preparation of C_{16} *Zwitterion.*—A mixture of crude Richter acid (15 g.), pyridine (70 c.c.), and acetic anhydride (100 c.c.) was heated on the steam-bath for 1 hour; a deep green solution was formed, from which a brownish-yellow, highly crystalline solid separated. The mixture was set aside overnight, and the solid then collected (13—14 g.); m. p. 215° (decomp.) after oven-drying. For analysis a sample was recrystallised from acetic acid–ligroin, from which the *substance* separated in small yellow polyhedra, m. p. 217° (decomp.). Other analytical samples were prepared directly from the pure reactants, and were rust-brown crystalline solids, m. p. 215—216° (decomp.) (Found: C, 64·85, 65·0, 65·9; H, 4·4, 3·55, 4·0; N, 14·5, 14·4. $C_{16}H_{11}O_5N_3$ requires C, 65·5; H, 3·8; N, 14·3. $C_{31}H_{16}O_4N_4$ requires C, 64·95; H, 4·1; N, 14·4%).

The substance was not appreciably soluble in cold water, but dissolved easily in aqueous sodium carbonate and in moderately concentrated hydrochloric acid. A suspension of the solid in aqueous dioxan gave an intensely bluish-purple solution, from which an amorphous blue solid was gradually precipitated after addition of a drop of concentrated ammonium hydroxide.

Reaction of C_{16} *Zwitterion with Alcohols.*—The substance was refluxed with the appropriate alcohol (methyl, 100 : 1, ethyl, 60 : 1; *iso*propyl, 120 : 1) for 1—1½ hours. In each case the original suspension gradually changed to a dark green, fluorescent solution, which was concentrated until crystallisation occurred. The *methyl* derivative separated from methyl alcohol in colourless polygonal plates, m. p. 143—144° (Found: C, 62·95, 62·25; H, 4·65, 4·8; N, 12·8, 13·0; OMe, 9·3, 9·45. $C_{17}H_{15}O_4N_3$ requires C, 62·75; H, 4·65; N, 12·9; OMe, 9·5. $C_{32}H_{20}O_5N_4$ requires C, 62·9; H, 4·8; N, 13·3; OMe, 7·4%). The *ethyl* derivative, from ethyl alcohol, formed very pale green, lustrous, irregular hexagons, m. p. 128—128·5° (Found: C, 64·05; H, 5·25; N, 12·35. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0; N, 12·4. $C_{33}H_{22}O_5N_4$ requires C, 63·6; H, 5·1; N, 12·9%). The iso*propyl* derivative crystallised from methyl alcohol in aggregates of faintly green, dull prisms, m. p. 130—131° (Found: C, 64·9; H, 5·45; N, 12·1. $C_{19}H_{19}O_4N_3$ requires C, 64·6; H, 5·4; N, 11·9. $C_{34}H_{24}O_5N_4$ requires C, 64·3; H, 5·4; N, 12·5%). These substances were insoluble in water, but soluble both in dilute sodium carbonate solution and in dilute hydrochloric acid. The ease of solution in alkali appeared to decrease somewhat in passing from the methyl to the *iso*propyl derivative.

Deacetylation of the Ether-acids (III).—(a) The methyl ether (III; R = Me) (1 g.) was refluxed with methyl alcohol (10 g.) and concentrated sulphuric acid (0·5 g.) for 4 hours; the solution gradually turned brown as the reaction proceeded. The product was neutralised with solid sodium bicarbonate, solvent removed in an exhausted desiccator, and water added to the residue, which was then extracted with ether. The dried and concentrated ethereal solution yielded 0·33 g. of lustrous yellow prismatic needles, m. p. 104—108°, which after several crystallisations from ether containing a little alcohol had m. p. 106—107° (Found: C, 63·1; H, 4·1; N, 15·05; OMe, 11·2. $C_{15}H_{13}O_3N_3$ requires C, 63·6; H, 4·6; N, 14·8; OMe, 10·95%). A sample prepared from an experiment in which ethyl alcohol was used in place of methyl alcohol was identical (m. p. and mixed m. p.) (Found: C, 63·05; H, 4·0; N, 14·85%). The substance was almost insoluble in cold water, but appreciably soluble in hot; it dissolved readily in moderately concentrated hydrochloric acid, and was insoluble in cold alkali carbonate and hydroxide; on warming with the latter, decomposition occurred (q.v.).

(b) The ethyl derivative (III; R = Et) was refluxed for 3—4 hours (0·75 g.) with concentrated sulphuric acid (0·37 g.) and either methyl or ethyl alcohol (7·5 g.) and the products worked up as in (a). In each case there was obtained *ca.* 0·4 g. of crude product, m. p. 135—139°, which after crystallisation from ether–alcohol formed large yellow lozenges, m. p. 140—141·5° [Found: (Methyl alcohol) C, 64·85; H, 4·7; N, 14·35; OMe, 15·3. (Ethyl alcohol) C, 65·15; H, 4·6; N, 14·6. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·1; OMe, 15·15%]. This compound, like that described in (a), showed basic properties towards hydrochloric acid, but was insoluble in cold sodium hydroxide; on warming the suspension a clear yellow solution was formed which gave no precipitate on cooling or acidification.

Reaction of C_{16} *Zwitterion with Aniline.*—A suspension of the powdered solid (1 g.) in benzene (13·5 c.c.) and aniline (1·5 c.c.) was heated under reflux; after 1 hour much suspended material remained, but this had almost completely dissolved after a further 1¾ hours of refluxing. The solution was diluted with ether and extracted thrice with aqueous sodium carbonate. The alkaline extract, after re-extraction with ether and clarification with charcoal, was made just acid to Congo red with dilute hydrochloric acid. The crude *acid* so obtained was washed, dried, and crystallised from ethyl acetate–ligroin (charcoal), giving 0·9 g. of almost pure material. An analytical sample formed soft, colourless needles, m. p. 161—162° after oven-drying (air-dried samples melted at 122—124° owing to solvation) (Found: C, 68·4; H, 4·6; N, 14·6. $C_{22}H_{16}O_3N_4$ requires C, 68·4; H, 4·7; N, 14·5%). The substance was very easily soluble in alcohol; it was only slightly soluble in cold 2N-hydrochloric acid, and the suspension decomposed when warmed (q.v.).

Preparation of Base, $C_{15}H_{13}O_3N_3$ (V), *and Substance,* $C_8H_{6(7)}O_5N$.—(a) The C_{16} zwitterion (0·3 g.) was refluxed in pyridine solution (5 c.c.) for 1 hour. The reaction proceeded, and the product was isolated, as described in (b) below, and the base (0·13 g.) identified by m. p. and mixed m. p.

(b) Crude Richter acid (5 g.) was refluxed for ½ hour with pyridine (15 c.c.) and acetic anhydride (5 c.c.). Vigorous gas evolution occurred during the first part of the reaction, and the usual green fluorescence, which is characteristic of experiments for the preparation of the zwitterion (II), gradually disappeared. The solvents were carefully distilled off at 15 mm., and the residual oil left over sulphuric acid in an exhausted desiccator; crystallisation occurred during 2 days. The crude solid was crystallised from alcohol (charcoal), 2·79 g. of the *base*, m. p. 158—161°, being obtained. An analytical sample separated from ethyl alcohol in colourless, shining leaflets, m. p. 161·5—162·5° (Found: C, 66·95; H, 4·6; N, 16·3. $C_{15}H_{13}O_3N_3$ requires C, 67·4; H, 4·9; N, 15·7%). The yield of base from a 2 g. run (reagents *pro rata*) was 1·2 g. The substance was insoluble in cold water and aqueous sodium hydroxide, and dissolved readily in 2N-hydrochloric acid.

On a larger scale, two 10 g. runs were carried out and worked up together; 14·6 g. (52%) of pure base were obtained after the mother-liquors had been worked up. The subsidiary crops of base were contaminated with a second *substance* which was comparatively sparingly soluble in hot alcohol: after several crystallisations from this solvent, it separated in long, straw-coloured, brittle needles, m. p. 259—261° (Found: C, 48·25; H, 3·15; N, 6·95. $C_8H_6O_5N$ requires C, 49·0; H, 3·1; N, 7·1. $C_8H_7O_5N$ requires C, 48·7; H, 3·55; N, 7·1%); yield, 0·5 g. of almost pure product from 20 g. of Richter acid. The substance was insoluble in 4N-ammonium hydroxide, slightly soluble in concentrated ammonium hydroxide, and soluble in warm 10% aqueous sodium hydroxide. A sodium salt separated from this solution, and dissolved on addition of water. The compound was unchanged (m. p. and mixed m. p.) after short boiling with 10% aqueous sodium hydroxide and subsequent acidification. It was slightly but appreciably soluble in boiling water, and crystallised well from the hot solution. Hot aqueous sodium carbonate was without chemical action. There was

evidence of hydrochloride formation in concentrated hydrochloric acid, but not with dilute acid, and the substance crystallised from its solution in concentrated acid on dilution with water.

(c) The crude zwitterion (2 g.) was refluxed for 1 hour with water (70 c.c.). A deep red solution was formed, but much material remained in suspension. The solution was filtered, and the filtrate and solid extracted separately with ether (boiling solvent was used for the solid). The extracts were bulked, dried, and evaporated, and the crude residue recrystallised from ether, from which the base separated in white prismatic needles, m. p. and mixed m. p. 160—161°.

Preparation of Base, $C_{13}H_9N_3$ (X).—(a) For preparative purposes, attention has been concentrated on the production of this substance by alkaline decomposition of the base, $C_{15}H_{13}O_2N_3$, described above. The following conditions gave an average yield (10 runs) of 60%, but the yield is slightly variable, and optimum conditions may not yet have been found. A suspension of the C_{15} base (1 g.) in 10% aqueous sodium hydroxide (20 c.c.) was heated for 10 minutes at 75°; a further 20 c.c. of alkali were then added, and the mixture maintained at 90° for 10 minutes, with frequent shaking from the beginning of the experiment. During this time an intensely pink colour developed, caused by the action of the aqueous alkali on a black oil (A) which tended to settle out. At the end of the 20 minutes' heating, no solid material could be seen, and the supernatant liquid was then decanted from the oil and heated almost to boiling; this caused the pink colour to fade, usually rapidly, and, when the colour had changed to a somewhat dirty brown, crystals of the new base separated on cooling. The black oil (A) was heated just to boiling with more sodium hydroxide solution (10 c.c.) for a few minutes, and water (20 c.c.) was added; the intense pink which appeared on adding the alkali soon faded, and the hot liquid was decanted from the remaining black oil, which was again treated with fresh alkali and water (10 c.c. and 20 c.c.) as before. After this third treatment, almost all oil had disappeared when the pink colour had faded. The three solutions were then combined, boiled for a few minutes (the total reaction time was about ¾ hour), and filtered cold. The crude base from 10 runs was crystallised from hot water, from which 4·65 g. of almost pure material (m. p. 151—152°) separated. The pure *base* crystallised from hot water in long, silky yellow needles, m. p. 152·5—153·5° after oven-drying, which caused the crystals to fall to a dull yellow powder. Air-dried (solvated) material melted at about 125—130° (Found for material dried in high vacuum at 50°: C, 63·75; H, 4·6; N, 17·25. $C_{13}H_9N_3,2H_2O$ requires C, 64·2; H, 5·35; N, 17·3%). The base was recovered unchanged after treatment with acetic anhydride (short boiling), and after attempts to prepare a semicarbazone, an anil, and an alkylidenemalonic acid under ordinary conditions. It dissolved readily in hot hydrochloric acid, and, on cooling, the *hydrochloride* separated; this was readily hydrolysed to the free base when it was washed with water. For analysis, the salt was recrystallised from equal volumes of concentrated acid and water and dried at 75°/0·4 mm.; it formed long, brittle, orange-brown needles, m. p. 219—221° (efferv.) after previous shrinking (Found: C, 57·3; H, 4·15; N, 15·55; Cl, 12·0. $C_{13}H_9N_3,HCl,2H_2O$ requires C, 55·8; H, 5·0; N, 15·0; Cl, 12·7%). The *picrate*, prepared from 70 mg. of the base and 80 mg. of picric acid, was very sparingly soluble in alcohol; it separated from acetic acid in fine soft yellow needles on rapid cooling (leaflets on slow cooling), m. p. 207—208° (Found: C, 51·75; H, 2·75; N, 18·85. $C_{13}H_9N_3,C_6H_3O_7N_3$ requires C, 52·3; H, 2·8; N, 19·3. $C_{13}H_9N_3,C_6H_3O_7N_3,2H_2O$ requires C, 48·3; H, 3·4; N, 17·8%). The *styphnate*, similarly prepared, was also very sparingly soluble in alcohol, and formed clusters of soft, lustrous, yellow needles, m. p. 203—204°, from slightly aqueous acetic acid (Found: C, 48·3; H, 2·45; N, 18·1. $C_{13}H_9N_3,C_6H_3O_8N_3,H_2O$ requires C, 48·5; H, 3·0; N, 17·9%).

In addition to the foregoing method of preparation, the same base was also isolated from the following experiments, identification being made in each case by m. p. and mixed m. p.

(b) The C_{15} base (150 mg.) was refluxed with 2N-hydrochloric acid (8 c.c.) for 1 hour, and the product isolated by basification with ammonia. (c) The methyl derivative (III; R = Me) was treated as in (b). (d) The methyl derivative (III; R = Me) (150 mg.) was heated with 5% sodium hydroxide (12 c.c.), first at 65°, then at 85°, and finally at 100°. A further 1 c.c. of alkali was added, and the C_{13} base isolated by cooling the solution after the deep pink coloration had faded. (e) The C_{15} zwitterion (100 mg.) was refluxed with 2N-hydrochloric acid (6 c.c.) for 5 hours, and the base obtained from the filtered solution by addition of ammonia. (f) When a few milligrams of the yellow base (VI; R = Me) were warmed with 2N-sodium hydroxide, the substance dissolved to a yellow solution which rapidly acquired the deep pink colour characteristic of the production of the C_{13} base, and this compound, as usual, separated from the cooled solution when the colour had faded. (g) The anilino-derivative (IV) (100 mg.) gave a red suspension when warmed with 2 c.c. of 2N-hydrochloric acid, and the liquid became oily on cooling. After 10 minutes' refluxing, a clear wine-red solution was produced, which remained clear when cooled. Addition of ammonia precipitated a dirty-blue solid, which on boiling with sodium hydroxide solution gave the usual transient deep pink coloration, and finally yielded the typical silky needles of the C_{13} base.

Isolation of Ampholyte, $C_{13}H_9ON_3$ (XIII; R = OH), *and Acid*, $C_{13}H_9O_2N_3$ (XIII; R = CO_2H).—The combined filtrates from the preparation of the base (X) [from 10 g. of (V)] were concentrated on the steam-bath to about 250 c.c.; a sodium salt separated, the solubilities of which in cold and in hot water were not greatly different. Careful acidification (Congo red) of an aqueous solution of this salt furnished the *substance* (XIII; R = OH), which formed straw-coloured prismatic needles, m. p. 186·5—187·5°, from alcohol (Found: C, 68·1; H, 4·6; N, 19·9. $C_{13}H_9ON_3$ requires C, 68·2; H, 4·3; N, 19·9. $C_{13}H_{10}ON_3$ requires C, 67·9; H, 4·8; N, 19·8%). The yield of nearly pure substance was 0·78 g.; it was insoluble in cold sodium bicarbonate solution and somewhat soluble in the hot, but dissolved when aqueous ammonia was added to the bicarbonate solution. It dissolved readily in warm 2N-hydrochloric acid; the hydrochloride, which separated rapidly on cooling, formed prisms or flat needles, m. p. 222—223° (decomp.). The salt was insoluble in water, apparently owing to hydrolysis to the original base.

The filtrate from the foregoing sodium salt was made just acid to Congo red with dilute hydrochloric acid (considerable buffering was observed), and the crude *acid* (XIII; R = CO_2H) which separated was collected (0·45 g.). A small amount of a relatively strong base [probably (XIII; R = OH)] was removed by extracting the solid with hot 2N-hydrochloric acid; the insoluble fraction, and the material which crystallised from the acid solution on cooling, were combined, dissolved in dilute aqueous ammonia, and precipitated by acidification of the filtered (charcoal) solution. Recrystallisation of the solid product from a little alcohol yielded the acid in soft, fine, straw-coloured needles, m. p. 169—170° (decomp.) (Found: C, 65·15; H, 3·7; N, 17·3. $C_{13}H_9O_2N_3$ requires C, 65·3; H, 3·8; N, 17·6%). The acid was insoluble in water, and readily soluble in cold aqueous sodium bicarbonate. It separated unchanged from hot 2N-hydrochloric acid, in which it was very sparingly soluble, although more readily than in water alone.

Identification of Acetic Acid as a Degradation Product of Base (V).—The filtrate from the above acid [(XIII; R = CO_2H)] (800—900 c.c.), was distilled until crystallisation occurred while hot; more water was then added and the distillation continued, about 1500 c.c. of distillate being collected. Of this, the first 1000 c.c. required 198·6 c.c. of 0·1953N-KOH, and the final 500 c.c., 15·6 c.c.; removal of volatile acid was therefore regarded as virtually complete, and was equivalent to 41·83 c.c. N-alkali [10 g. of base (V) require 37·45 c.c.]. The resultant sodium salt was treated with 8·5 g. of *S*-benzylthiuronium chloride in slightly aqueous alcoholic solution; only 4·85 g. of *S*-benzylthiuronium acetate could be isolated [m. p. and mixed m. p. 143—144° (from methyl ethyl ketone; Bergel *et al.*, *J.*, 1944, 418, give m. p. 143—144°; Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004, gives m. p. 134°)], but considerable hydrolysis to

benzylthiol occurred during examination of the material, and there was no evidence of the presence of appreciable amounts of any other organic acid.

Preparation of Base, $C_{12}H_9N_3$ (XIII; R = H).—The acid (XIII; R = CO_2H) (75 mg.) was decarboxylated by heating it in an open tube at 180—185° (bath temp.) for a few minutes. The cooled melt was crystallised from ammoniacal alcohol, from which the *base* separated in long, soft, colourless needles, m. p. 113—114°, sparingly soluble in cold alcohol and in hot and cold 2N-hydrochloric acid, almost insoluble in hot water, and fairly easily soluble in warm 6N-hydrochloric acid (Found: C, 73·85; H, 4·7; N, 21·05. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6; N, 21·5%).

Reaction between Richter Acid, Quinoline, and Acetic Anhydride.—The pure acid (0·5 g.) was heated on the steam bath for 2½ hours with quinoline (8 c.c.) and acetic anhydride (6 c.c.), and set aside overnight. The brown solid which separated was collected, and refluxed with alcohol (100 c.c.) for 2 hours; the resultant green fluorescent solution was concentrated, and the *ethyl* derivative crystallised from alcohol, from which it formed colourless fern-like blades, m. p. 170—171° (Found: C, 67·8; H, 5·1; N, 11·1. $C_{22}H_{19}O_4N_3$ requires C, 67·85; H, 4·9; N, 10·8. $C_{21}H_{16}O_5N_4$ requires C, 69·6; H, 4·9; N, 10·5%).

Oxidation of Base, $C_{12}H_9N_3$.—A 2% solution of potassium permanganate (225 c.c.) was added during 1 hour to a suspension of the base (1·5 g.) in water (100 c.c.). Oxidation was rapid, but to ensure its completion the mixture was warmed to 45° for 10 minutes, after which alcohol was added to remove excess permanganate. The suspension was filtered, and the filtrate made barely acid to Congo red with hydrochloric acid and extracted with ether; no material could be extracted at a higher pH. When the extraction appeared to be complete, the aqueous solution was made distinctly acid to Congo red if its colour was deeper than pale yellow; in such cases re-extraction gave a further yield of ether-soluble material. Concentration of the dried, orange-yellow ethereal extract gave a crystalline residue; this was combined with the product from a duplicate experiment, and, after one crystallisation from ethyl acetate, yielded heavy orange-red prisms (1·8 g.), m. p. 146—147°. The *substance* (XIV) separated characteristically from water, in which it is sparingly soluble in the cold, as a mixture of voluminous white and denser red needles (the latter tended to predominate on standing) of unchanged m. p. (Found: C, 63·9, 63·6; H, 3·85, 3·9; N, 18·8, 18·8. $C_{12}H_9O_2N_3$ requires C, 63·45; H, 4·0; N, 18·5%). Oxidations on a smaller scale gave similar results. A suspension of the substance in cold water dissolved on addition of aqueous sodium bicarbonate or dilute hydrochloric acid; the solutions in acid and alkali were orange in colour. The *picrate* (90 mg.), prepared from a hot solution of 50 mg. of the substance in 14 c.c. of water and 6 c.c. of saturated aqueous picric acid, formed long, lustrous red needles, m. p. 172—174°, unchanged by several crystallisations from water. The colour lightened to orange after drying (Found: C, 47·9; H, 2·7; N, 18·45. $C_{12}H_9O_2N_3,C_6H_3O_7N_3$ requires C, 47·4; H, 2·65; N, 18·4%).

Action of Hydrochloric Acid on (XIV).—The compound (1·5 g.) was refluxed for 3 hours with a mixture of equal volumes of water and concentrated hydrochloric acid (12·5 c.c.). The dark brown solution crystallised on cooling, and the solid (1·05 g.) was dissolved by treatment with hot 2N-sodium hydroxide followed by repeated digestion of the insoluble portion with hot water. The alkaline and aqueous solutions were combined, filtered (charcoal) from a trace of insoluble matter, and made just acid to Congo red with dilute hydrochloric acid. The precipitated solid (0·75 g.) was collected and washed (evaporation of the filtrate gave some tarry material which was discarded), and digested with boiling alcohol (15 c.c.). After a second digestion, the high-melting component of the mixture was obtained almost pure (0·33 g., m. p. 250—251°); the pure *substance* crystallised rapidly from acetic acid in small, slightly discoloured prisms, m. p. 253—254° (Found: C, 58·05; H, 3·25; N, 17·6. $C_{11}H_7O_3N_3$ requires C, 57·65; H, 3·1; N, 18·3. $C_{12}H_9O_2N_3$ and $C_6H_6O_3N_2$ require C, 59·3; H, 3·7; N, 17·3%). The substance was almost insoluble in boiling water, sparingly soluble in hot 2N-, and fairly easily soluble in hot 6N-hydrochloric acid. The yellow sodium salt was only formed to a slight extent in presence of warm aqueous bicarbonate, but more easily with warm sodium carbonate and sodium hydroxide solutions; this salt was sparingly soluble in water, and less so in alkali solutions.

The alcoholic filtrates from the above compound were combined and concentrated, and the crude acid, m. p. 175—185° (0·27 g.), crystallised repeatedly from alcohol (charcoal), after removal of a small quantity of insoluble material. The *acid* formed long, soft, orange-pink needles, m. p. 194—195°, very sparingly soluble in hot water, easily soluble in aqueous sodium bicarbonate and other alkalis and in hydrochloric acid giving orange solutions (that in dilute hydrochloric acid crystallised on cooling) (Found: C, 54·95; H, 3·0; N, 16·05. $C_{12}H_9O_4N_3$ requires C, 55·6; H, 3·5; N, 16·2. $C_6H_5O_3N_2$ requires C, 54·2; H, 2·8; N, 15·8%). A solution of the acid (110 mg.) in concentrated hydrochloric acid (1 c.c.) and water (1 c.c.) was refluxed for 3½ hours; no material separated on cooling. Solvent was removed in an evacuated desiccator, and, on treatment of the residue with aqueous sodium hydroxide, all but a trace dissolved. Acidification (to Congo red) of the filtered solution followed by crystallisation of the solid from alcohol (charcoal) gave 30 mg. of unchanged material (m. p. 185—187°, mixed m. p. intermediate) as the least soluble fraction. The filtrate was evaporated to dryness, and the residue was found to be freely soluble in aqueous bicarbonate except for a trace of insoluble matter, thus indicating the absence of significant quantities of the substance, m. p. 254°, described above.

Derivatives of Product from Reaction between 4-Hydroxy-6-methoxycinnoline-3-carboxylic Acid, Pyridine, and Acetic Anhydride.—The crude cinnolinecarboxylic acid (5 g.) was heated at 95° for 1½ hours with pyridine (35 c.c.) and acetic anhydride (40 c.c.). After standing overnight at 0°, the solution had deposited 3·65 g. of a lustrous, brown crystalline solid, m. p. 214—216° (decomp.). No attempt was made to purify this substance, portions of which were treated as follows:

(a) 0·5 G. was refluxed with methyl alcohol (100 c.c.) for 2 hours. The *methyl* derivative (0·44 g.), obtained by concentration of the green fluorescent solution, separated from methyl alcohol in clusters of glistening, colourless, prismatic needles, m. p. 179—180° to a dark green liquid (Found: C, 60·8; H, 5·1; N, 12·1; OMe, 16·7. $C_{18}H_{17}O_5N_3$ requires C, 60·8; H, 4·8; N, 11·8; OMe, 17·45%).

(b) A similar experiment to (a) using ethyl instead of methyl alcohol gave 0·3 g. of a dirty white solid, m. p. 65—75°. This m. p. is unexpectedly low, and the substance has not yet been purified.

(c) 1 G. was refluxed for 1 hour with pyridine (16 c.c.), solvent removed at 15 mm., and the residual oil left to crystallise in an exhausted desiccator. The product, after several crystallisations from alcohol, formed clusters of pale yellow prismatic needles, m. p. 131·5—132·5° (Found: C, 64·5; H, 4·7; N, 14·4; OMe, 10·4. $C_{16}H_{13}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·1; OMe, 10·4%).

The authors are indebted to Imperial Chemical Industries, Limited, Dyestuffs Division, for financial and other assistance in support of this investigation, and to the Council of the Durham Colleges for a grant from the Research Fund. Acknowledgments are also due to the Medical Research Council for financial support in the final stages of this work.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
DEPARTMENT OF CHEMOTHERAPY, LIVERPOOL SCHOOL OF TROPICAL MEDICINE. [*Received, October 25th*, 1945.]

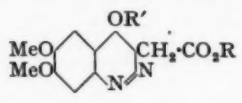
93. *Cinnolines. Part VI. Derivatives of 4-Hydroxy-6 : 7-dimethoxycinnoline-3-acetic Acid.*

By J. C. E. Simpson.

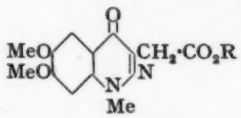
A few simple functional derivatives of 4-hydroxy-6 : 7-dimethoxycinnoline-3-acetic acid are described. Both O- and N-*methyl* ethers are formed by the action of methyl sulphate and alkali on the acid; these are produced in approximately equal amounts, and are converted by esterification into the corresponding *ether-esters*. The two isomeric series are designated α- and *β*-, and, although corresponding members differ markedly in chemical properties (basicity, ease of decarboxylation), it has not proved possible to distinguish with certainty between the alternative structures for each substance.

The preparation of the substance named in the title has already been described (Schofield and Simpson, *J.*, 1945, 520), but the study of its reactions originally planned has had to be postponed after the derivatives described below had been prepared.

Treatment of the acid (I; R = R′ = H) with methyl sulphate and alkali gave a mixture of two isomeric *ether-acids*, (I; R = H; R′ = Me) and (II; R = H), designated for convenience α- and β-, from which only the α-compound, m. p. 260° (decomp.), could be obtained pure. Esterification of the mixture with methyl alcohol and sulphuric acid yielded the corresponding mixture of *ether-esters* (I; R = R′ = Me) and (II; R = Me), which was separated without difficulty into the pure α- and β-isomers. Each of these was readily hydrolysed by dilute hydrochloric acid, but whereas the α-ether-acid separated directly from the reaction solution, hydrolysis of the β-compound gave a well-defined *hydrochloride* of the β-ether-acid. This salt was soluble in hot water, and from the solution the pure β-ether-acid separated after a few minutes; re-esterification of this acid yielded the parent ester, identical with that prepared by fractionation of the original mixture of ether-esters. The α- and β-ether-acids also behaved differently when heated; the β-compound was stable well above its melting point, but the α-isomer readily lost carbon dioxide at the melting point and yielded a *base* (III or IV), which is provisionally designated the " α-ether." This substance formed a hydrochloride, and a slight degree of quaternisation seemed to occur when it was refluxed with ethyl iodide in alcoholic solution.



(I.)



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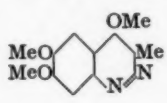
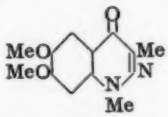


(III.)



(IV.)

It was hoped that methoxyl determinations would enable definite structures to be assigned to substances of the α- and β-series by virtue of the ease with which *O*-dealkylation is usually effected as compared with *N*-dealkylation. However, estimations on the substance (III or IV) and on the β-ether-acid, as representatives of each series, were unsatisfactory, being appreciably below the theoretical value for two methoxyl groups. No systematic study appears to have been made of the factors which affect the reactivity of methoxyl groups on C_4 in nitrogen heterocyclic compounds, but the inertness encountered here, both in the Zeisel estimations and in the acid hydrolysis of the α- and β-ether-esters, contrasts sharply with the extreme reactivity displayed by C_4 alkoxyl groups in various quinazoline derivatives (Bogert and May, *J. Amer. Chem. Soc.*, 1909, **31**, 507; Lange and Sheibley, *ibid.*, 1932, **54**, 1994, 4305; 1933, **55**, 1188).

The available chemical evidence, although favouring the *N*-methylcinnolone structure for the α-series, is not decisive. The greater basicity of the β- as compared with the α-ether-acid cannot be used as evidence of the *O*-ether structure for the latter by analogy with the absence of basic properties in the hydroxy-acid (I; R = R′ = H) of similar fine structure (Schofield and Simpson, *loc. cit.*), because 4-methoxycinnoline is decidedly more basic than 4-hydroxycinnoline (a suspension of the former in cold water dissolves immediately on addition of a drop of 2N-hydrochloric acid, but the hydroxycinnoline dissolves only slowly on warming with 2N-acid), and it is therefore probable that a similar difference would be found between the two acids (I; R = R′ = H) and (I; R = H, R′ = Me). Fusion of the α-ether with phthalic anhydride, both with and without zinc chloride [the C_3-methyl group should be reactive in a substance of structure (IV), but not in one of structure (III)], gave no positive result. Attempted diagnosis of the structure of this substance by means of a mixture of phosphorus pentachloride and phosphorus oxychloride was also unsuccessful; it is well established (Fischer and Guthmann, *J. pr. Chem.*, 1916, **93**, 379; Thielepape, *Ber.*, 1922, **55**, 127; Thielepape and Fulde, *ibid.*, 1939, **72**, 1432) that *N*-methyl-α-quinolones are smoothly converted into α-chloroquinolines by these reagents, but, in the present case, almost the whole of the material was converted into a highly-coloured water-soluble product after basification of the diluted reaction-mixture. This behaviour is not obviously explicable on the basis of structure (III), but could be explained on the assumption that the reaction with (IV) gives the 4-chloromethochloride as primary product, as a number of 4-substituted quaternary cinnolinium salts have been observed in this laboratory to yield intensely coloured solutions on treatment with alkali (unpublished). Finally, the extreme ease with which the α-ether acid undergoes decarboxylation also points to the *N*-ether structure for the α-series, because the acid (I, R = R′ = H), although of higher decomposition point, does not behave similarly, and a crystalline product could not be obtained when decarboxylation of the acid was attempted with quinoline and copper carbonate.

EXPERIMENTAL.

(Melting points are uncorrected.)

Preparation of Mixed α- and β-Ether-acids.—A solution of 4-hydroxy-6 : 7-dimethoxycinnoline-3-acetic acid (50 g.) in 10% sodium hydroxide (400 c.c.) and water (200 c.c.) was treated with methyl sulphate (70 c.c.), added in portions with shaking in a stoppered flask at 50—60°. Excess of sodium hydroxide solution was then added, after which the clear solution was cooled somewhat and made acid to Congo red with dilute hydrochloric acid. The solid product, which invariably separated in two distinct crops, was collected and washed (yield, 40·5 g.). Several crystallisations of a portion of this material from aqueous acetic acid gave the pure *α-ether-acid* as minute colourless needles, m. p. 260—261° (efferv.) (dependent on the rate of heating) (Found : C, 55·2; H, 5·1. $C_{13}H_{14}O_5N_2$ requires C, 56·1; H, 5·1%). The acid was easily soluble in cold aqueous sodium carbonate and not appreciably soluble in hot alcohol or hot 2N-nitric acid. The acidified filtrate from the mixed isomers was combined with that from a 25 g. experiment (which gave 20·5 g. of mixed solids), and excess of sodium acetate was added, followed, after evaporation to about 400 c.c., by 12 g. of picric acid; the mixture of picrates (14·5 g.; m. p. 255—260°) which separated was not investigated.

Preparation of α- and β-Ether-esters.—The foregoing mixture of ether-acids (40·5 g.) was refluxed for 3½ hours with methanol (500 c.c.) and concentrated sulphuric acid (20 c.c.). Excess of solid sodium bicarbonate was then added, and most of the methanol removed by evaporation. The residue, after dilution with water and a little aqueous sodium carbonate, was extracted four times with chloroform. The extract was dried (sodium sulphate) and evaporated, and the residue crystallised from alcohol, yielding 18·1 g. of almost pure *α-ether-ester*, m. p. 185—186°. An analytical sample formed long, pale yellow needles, m. p. 186—187°, only moderately soluble in hot alcohol, and appreciably soluble in hot water (Found : C, 57·5; H, 5·3. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5%). For hydrolysis, the ester (15 g.) was heated on the steam-bath with 2N-hydrochloric acid (240 c.c.) for 1 hour. The solid rapidly dissolved, and this was soon followed by crystallisation of the product, which was filtered cold, washed and dried; yield, 13·4 g., m. p. 261—262° (efferv.) alone and mixed with the α-ether-acid already described.

The alcoholic filtrate from the α-ether-ester was combined with that from a similar experiment, in which 21·5 g. of mixed ether-acids had been esterified, and the solvent was removed. Crystallisation of the residue from acetone readily yielded the pure *β-ether-ester* (20·8 g.) as brittle yellow prismatic needles, m. p. 184—185° (160—170° when mixed with the α-isomer); occasionally this substance separated from acetone, in which it was rather sparingly soluble, as sheaves of long, silky needles, m. p. 188—189° (Found : C, 57·95; H, 5·3. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5%).

Preparation of β-Ether-acid.—The β-ether-ester dissolved rapidly at room temperature in 30 parts of 2N-hydrochloric acid. The ester (10 g.) was heated for ¾ hour on the steam-bath with the acid (100 c.c.) and crystallisation of the product (9 g.) was induced by adding 30 c.c. of concentrated hydrochloric acid (the same product also separated from 2N-acid alone, but the yield was apt to be lower). This *hydrochloride* of the β-ether-acid formed small, colourless, glassy cubes, m. p. 252—253° (decomp.). For analysis it was recrystallised from a mixture of dilute and a little concentrated hydrochloric acid, and washed with alcohol (Found : C, 49·6; H, 4·7; N, 9·15; Cl, 12·05. $C_{13}H_{15}O_5N_2Cl$ requires C, 49·6; H, 4·8; N, 8·9; Cl, 11·3%). When the salt (9 g.) was warmed with water (*ca.* 100 c.c.) it dissolved to a clear yellow solution, which quickly deposited a mass of needles (8 g.) of the free *β-ether-acid*, m. p. 241—243°. An analytical sample of this substance separated from dilute acetic acid in small, soft, colourless needles, m. p. 244—245° (230—235° when mixed with the α-isomer), not appreciably soluble in hot water, acetone, chloroform, or alcohol, and easily soluble in pyridine, glacial acetic acid, aqueous sodium carbonate, and aqueous sodium acetate. The acid showed no tendency to lose carbon dioxide, and was stable even when heated to 310° [Found : C, 55·6; H, 5·0; N, 10·35; OMe, 20·9. $C_{13}H_{14}O_5N_2$ requires C, 56·1; H, 5·1; N, 10·1; OMe (2), 22·3%]. Esterification by the method described for the mixed ether-acids gave the β-ether-ester as sole product (identified by m. p. and mixed m. p.).

Preparation of α-Ether from α-Ether-acid.—(a) The acid (1 g.) was heated in an open tube in an oil-bath; decarboxylation set in suddenly at 280° (bath temp.) and was complete in a few minutes. The brown melt set to a hard crystalline mass on cooling, a solution of which in alcohol yielded 0·6 g. of discoloured stout prismatic needles, m. p. 228—230°, of the *α-ether*. An analytical sample formed small yellow prisms, m. p. 229—230°; the substance sometimes separated from supersaturated solutions in fine soft needles [Found : C, 60·85; H, 5·8; N, 12·15; OMe, 23·7. $C_{13}H_{14}O_5N_2$ requires C, 61·5; H, 6·0; N, 12·0; OMe (2), 26·5%]. The substance was fairly easily soluble in hot alcohol, and insoluble in ether, water, alkalis, and dilute acids. When it was heated with a mixture of acetic acid and 6N-hydrochloric acid, a sparingly soluble hydrochloride, m. p. 229—230° (decomp.) (220—225° when mixed with the original substance), separated on cooling. That this was the hydrochloride, and not the product of any further reaction, was shown by suspending it in water and adding aqueous ammonia; the solid dissolved almost completely, followed by crystallisation of the original base, m. p. and mixed m. p. 230—231°. After the base (0·2 g.) had been refluxed for 4½ hours with ethyl iodide (2 c.c.) and alcohol (4 c.c.), the product which separated on cooling had m. p. 205° (efferv.), but gave no depression when mixed with the original material.

(b) The acid (1·1 g.) was heated with benzophenone (3·3 g.) (cf. Schofield and Simpson, *loc. cit.*) in an open tube in an oil-bath. The solid remained in suspension until a bath temperature of 260—270° was reached; decarboxylation then occurred and a clear yellow solution was formed, which quickly turned brown. After a further 5 minutes the product was isolated from the cooled melt by digestion with ether; yield 0·75 g., m. p. 226—228° alone and when mixed with a sample prepared by method (a).

The author is indebted to the Council of the Durham Colleges for a grant from the Research Fund, and to Imperial Chemical Industries Limited, Dyestuffs Division, for their support of this investigation.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, October 25th*, 1945.]

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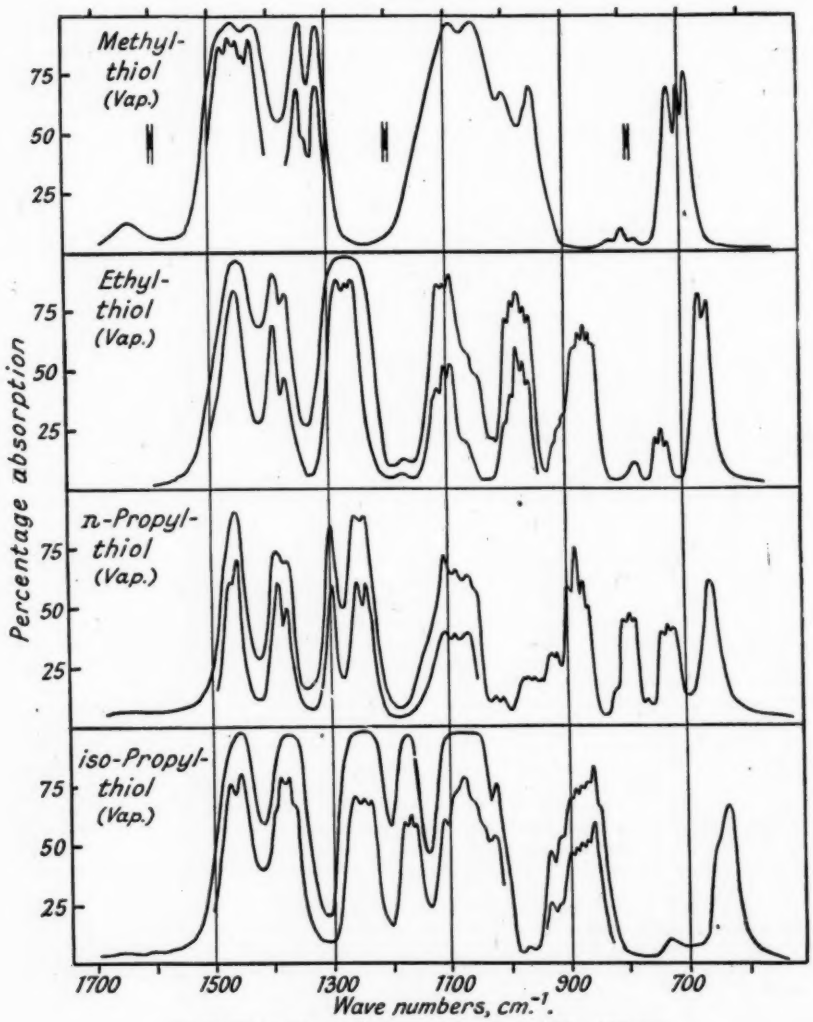
94. *The Infra-red Spectra of Thiols, Sulphides, and Disulphides.*

By I. F. TROTTER and H. W. THOMPSON.

The infra-red absorption spectra of a number of alkylthiols, alkyl sulphides, and alkyl and aryl disulphides have been measured. The results have been correlated with the Raman spectra, and in some cases a partial assignment of normal vibration frequencies has been made. The derivation of frequencies which are characteristic of vibrations of C–S and S–S linkages has been discussed. Some of the infra-red bands show a partially resolved rotational structure.

In some recent papers from this laboratory attempts have been made to correlate the infra-red spectra of complex molecules with the presence of particular atomic groupings. It has been emphasised that if such structural diagnosis is to be successful, it must be based upon a preliminary survey of the spectra of series of related simpler molecules, from which vibration bands can be found which are characteristic of particular groups in the skeleton. In connexion with infra-red measurements on vulcanised rubbers and the mechanism of vulcanisation by means of sulphur chloride (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 276) we have recently measured the spectra of a number of thiols, alkyl and aryl sulphides and disulphides, from which it was hoped to discover key vibration frequencies for the C–S and S–S bonds. The spectra of

Fig. 1.



Methylthiol, 27 *cm. path with pressures* 200—300 *mm.*
Ethylthiol, 20 *cm. path with pressures* 100—200 *mm.*
n-*Propylthiol*, 27 *cm. path with pressures* 100—150 *mm.*
iso*Propylthiol*, 27 *cm. path with pressures* 100—200 *mm.*

methylthiol and dimethyl sulphide were examined in this laboratory some years ago (*ibid.*, 1940, **36**, 812; 1941, **37**, 1), but in view of the greater resolving power now available these measurements have been repeated.

Although the work has so far failed to give an unequivocal decision on the points for which it was originally planned, the spectra were useful for general purposes of reference, and in providing data upon which analyses could be based if required. Further, the resolution of the rotational fine structure and band contour of some of the vibration bands is not without value in the assignment of the frequencies to normal modes of these molecules.

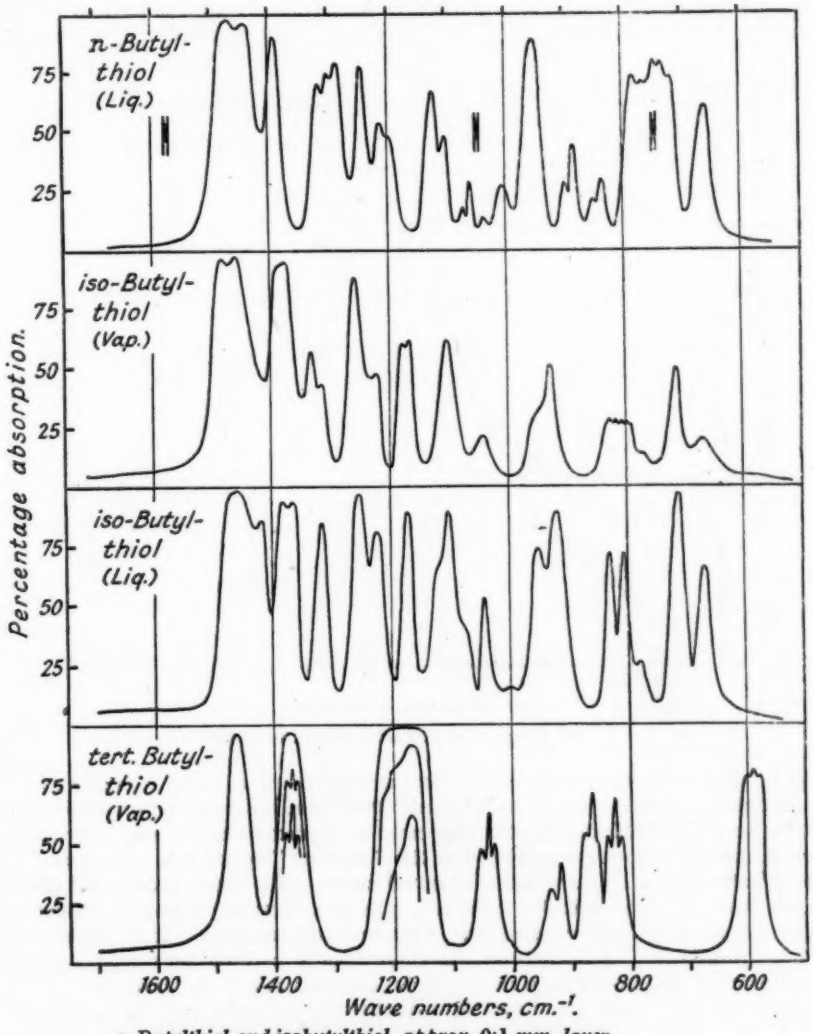
Experimental.

For the range 2—14 μ an automatically recording spectrometer built in this laboratory was used, with a rock-salt prism (Whiffen and Thompson, J., 1945, 268). For the range 14—20 μ a survey was made on this recorder by using a

prism of potassium bromide, but owing to the irregular background in this region resulting from absorption by atmospheric water vapour and carbon dioxide, better results were obtained by using a manually operated Hilger D 88 spectrometer with sylvine prism. "False energy" was minimised by the use of either quartz or rock-salt shutters in front of the entrance slit. The effective slit widths used are shown on the diagrams.

The vapours were contained in cylindrical glass tubes with flanged ends, on to which plates of rock-salt or potassium bromide were sealed with a hard stop-cock grease. Liquids were examined in conventional cells made by separating a pair of rock-salt or bromide plates with a suitable washer.

FIG. 2.



n-*Butylthiol and* iso*butylthiol, approx.* 0·1 *mm. layer.*
iso*Butylthiol (vap.),* 27 *cm. path with* 100 *mm. pressure.*
tert.-*Butylthiol (vap.),* 27 *cm. path with* 40—150 *mm. pressures.*

The compounds used were commercial samples, purified by careful fractionation. As a rule the middle fraction was taken, but in some cases the spectra of other fractions were also measured as a check on purity. Methylthiol was purified by fractionation of a large sample in a vacuum. The b. p.'s (uncorr.) of the other samples finally used were as follows:

Ethylthiol	35·5°	Dimethyl sulphide	43·0°
n-Propylthiol	67·5—68	Methyl ethyl sulphide	62·5—63·5
*iso*Propylthiol	51—51·5	Diethyl sulphide	90·0
n-Butylthiol	97·5	Dimethyl disulphide	108—109/753 mm.
*iso*Butylthiol	88—88·5	Diethyl disulphide	65/40 mm.
tert.-Butylthiol	64·5	Di-*n*-propyl disulphide	99/40 mm.

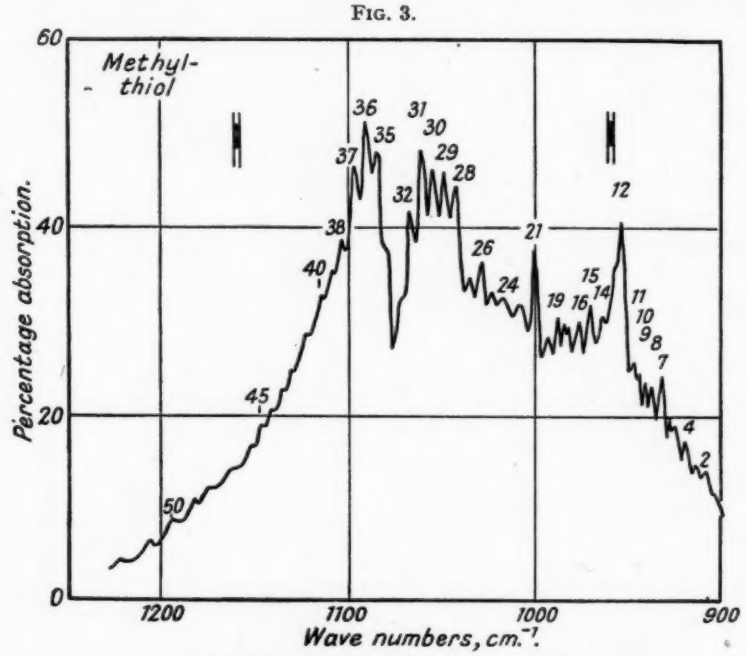
Solid dibenzyl disulphide was recrystallised from carbon disulphide; m. p. 69°. This substance was measured both as a solid layer melted on to a rock-salt plate, and also as a powder after being ground with medicinal paraffin.

RESULTS AND DISCUSSIONS.

(1) *Thiols.*—The spectra of the thiols between 6 and 20 μ are shown in Figs. 1 and 2. The curves for the region 2—6 μ are not shown, since they do not contribute materially to the interpretations, although it may

be noted that a few minor differences in the positions of overtones and combination bands in this spectral range might be useful for analytical work. In the range 2—6 μ the only significant bands arise from the fundamentals associated with C–H stretching (2800—3000 cm.$^{-1}$), and with S–H stretching (about 2580 cm.$^{-1}$). The spectrum of methylthiol vapour agrees in all essentials with that given previously, but the improved resolution provides additional confirmation of the assignment of frequencies to the different types of mode. Thus the bands at 708, 800, 1330, and 2580 have the expected " parallel " type contour, with a spacing between P and R branches of about 33 cm.$^{-1}$. The absorption in the region 900—1200 cm.$^{-1}$ previously attributed to a pair of perpendicular type vibrations, is now seen to be resolved into a galaxy of Q branches, confirming this assignment. This region is shown on an enlarged scale in Fig. 3, and the frequencies of the peaks observed

FIG. 3.



Methylthiol, 27 cm. path, 75 mm. pressure.

are given in Table I. It is seen that the distribution of intensities in these bands is so complex as to give no clue to a detailed interpretation, but about 950 and 1060 seem reasonably probable values for the centres of the two perpendicular bands. Methylthiol is very nearly a symmetrical rotator, having $I_A \sim I_B \sim 60 \times 10^{-40}$ and $I_C \sim 5{\cdot}4 \times 10^{-40}$ g. cm.^{2}. For a symmetrical top the " normal " spacing of Q branches in a perpendicular type band will be $(h/4\pi^2)(1/I_C - 1/I_A)$, which is about 9 cm.$^{-1}$. The spacing actually observed is much less than this, and shows that the perpendicular type bands have a complex structure. Such undue complexity is surprising in view of the close approximation to a symmetrical rotator. It seems probable that complex vibrational rotational interaction is occurring. If these bands can be measured with the much higher resolving power of a grating spectrometer, a more precise analysis might be profitable.

The bands at 1430 and 1475 cm.$^{-1}$ also have signs of the perpendicular type structure, as expected.

TABLE I.

Number of line.	Position, cm.$^{-1}$.	Number of line.	Position, cm.$^{-1}$.	Number of line.	Position, cm.$^{-1}$.	Number of line.	Position, cm.$^{-1}$.	Number of line.	Position, cm.$^{-1}$.
1	902	12	953	23	1009	33	1071	43	1135
2	908	13	957	24	1017	34	1080	44	1141
3	913	14	962	25	1023	35	1084	45	1146
4	920	15	970	26	1029	36	1090	46	1152
5	924	16	976	27	1035	37	1096	47	1160
6	927	17	982	28	1042	38	1103	48	1174
7	931	18	984	29	1048	39	1109	49	1183
8	937	19	988	30	1054	40	1114	50	1195
9	940	20	993	31	1060	41	1122	51	1207
10	944	21	1000	32	1066	42	1130	52	1222
11	947	22	1006						

The results for ethylthiol agree substantially with those of Coblentz (" Investigations of Infra-red Spectra," 1905, Vol. 1), but show more detail. Also there is very close agreement between the infra-red frequencies and those obtained from the Raman spectrum, from which Venkateswaran (*Indian J. Physics*, 1930, **5**, 219)

deduced the following intervals: 333(2), 659(10), 739(0*d*), 874(0), 965(0), 1054(1*b*), 1263(1*b*), 1449(3*b*), 2573(10), 2872(5*b*), 2933(10*b*), 2968(7*b*). The strong infra-red bands near 1100 and 1400 cm.$^{-1}$ have no analogues in the Raman spectrum. Many of the infra-red bands show a partially resolved and rather complex rotational contour, but it is impossible to correlate it with the molecular structure.

A rough measurement of the infra-red spectrum of *n*-propylthiol has been reported by Bell (*Ber.*, 1927, **60**, 1749) and by Ellis (*J. Amer. Chem. Soc.*, 1928, **50**, 2113). The present results agree satisfactorily, but again show more detail. Here, too, many infra-red frequencies agree with the Raman intervals found by Venkateswaran, namely: 367(3), 652(4), 695(1*d*), 730(0*d*), 883(0), 964(0), 1033(2*b*), 1299(1*b*), 1441(2*b*), 2575(8*d*), 2874(4*b*), 2930(8*b*), 2966(5*b*). As might be expected with the increase in molecular complexity, however, the coincidences are less complete than with methyl- or ethyl-thiol.

The results for *iso*propylthiol agree closely with the Raman spectrum recorded by Kohlrausch, Dadieu, and Pongratz (*Wien. Ber.*, 1932, **141**, II*a*, 276), who found the following displacements: 261(2), 335(4), 414(2), 488(4), 626(8*b*), 855(2*b*), 886(3*b*), 1050(1), 1145(1), 1251(1*b*), 1307(1), 1450(5*b*), 2567(3), 2866(4), 2915(5*b*), 2962(3*b*). With *n*-butylthiol there is similar concordance with the infra-red measurements of Bell (*loc. cit.*) and with the Raman intervals deduced by Venkateswaran, namely, 298(1), 333(2), 437(0), 656(6), 707(0*b*), 843(0), 951(1), 1049(1*b*), 1106(0), 1296(2*b*), 1361(0*b*), 1438(8*b*), 2574(10), 2869(8*b*), 2905(7*b*), 2934(10*b*), 2964(6*b*).

In Fig. 2 the spectrum of *iso*butylthiol is shown both for the vapour and for the liquid. There is very close agreement with the Raman data of Venkateswaran (*loc. cit.*) and of Kopper, Seka, and Kohlrausch (*Wien. Ber.*, 1932, **141**, II*a*, 465), the latter giving the following intervals: 224(1), 339(4), 402(2), 427(3), 668(3), 708(5), 770(2), 801(2), 824(2), 924(1), 955(3), 1108(2), 1216(2), 1250(1), 1319(1), 1336(1),1370($\frac{1}{2}$), 1423(2*b*), 1452(4*b*), 2573(8*b*), 2829(0), 2872(8), 2919(5), 2958(10). It can be seen that marked changes of intensity and to a less extent of wave-length occur in the infra-red spectrum on passing from the liquid to the vapour. Such alterations of intensity with change of state are neither uncommon nor inexplicable, and are at present being examined in greater detail with various polar and non-polar compounds. It is usually found that with the liquid or solid phase the bands tend to be sharper than with the vapour.

The infra-red spectrum given in Fig. 2 for *tert.*-butylthiol agrees well with the Raman data of Köppl and Kohlrausch (*Wien. Ber.*, 1933, **142**, II*b*, 477) who found the following intervals: 295(3), 368(5), 395(1), 445($\frac{1}{2}$), 587(10), 819(6), 866(2), 930(2), 1030($\frac{1}{2}$), 1103(0), 1160(4), 1177(3), 1218(3*b*), 1449(5*b*), 2570(7), 2714(2), 2775(1), 2864(4), 2898(6), 2924(8). With this molecule many of the infra-red bands found for the vapour show a well-marked contour of the *P*–*Q*–*R* branch type which might well arise owing to the close approximation of this molecule to a symmetrical rotator. Rough calculation of the separation of the *P* and *R* maxima using the expression of Dennison and Gerhard $[S(\beta)/\pi]\sqrt{kT/I_A}$ gives a value of about 18 cm.$^{-1}$, which agrees with that observed within the error of measurement.

All the above thiols show an infra-red band at about 2580 cm.$^{-1}$ which is connected with a stretching vibration of the S–H bond. The intensity of this band is comparatively low. Also, each of the compounds shows bands between 2800 and 3000 cm.$^{-1}$ which are associated with the C–H bond stretching modes, but we have not attempted to explore them with high resolving power.

The main point of general interest is whether the frequency associated with a stretching vibration of the C–S bond remains approximately constant throughout the series of thiols. In methylthiol this lies at 705 cm.$^{-1}$ and in the ethyl derivative the corresponding band lies at 660 cm.$^{-1}$, the intense Raman interval being 659. With some of the higher homologues there are several infra-red bands in the range 550—750 cm.$^{-1}$, but in deciding which is due to the C–S stretching mode the Raman data are helpful in that the C–S stretching frequency is strong in the Raman effect. Inspection of the data shows that in all cases except that of *iso*butylthiol the assignment given in Table II is convincing. With *iso*butylthiol the infra-red bands at 672 and 708 correspond to Raman intervals 668(3) and 708(5), and it is not clear which of the two frequencies should be assigned to the C–S stretching mode.

TABLE II.

Thiol.	Infra-red, cm.$^{-1}$.	Raman, cm.$^{-1}$.	Thiol.	Infra-red, cm.$^{-1}$.	Raman, cm.$^{-1}$.
Methyl	705	702	*n*-Butyl	658	656
Ethyl	660	659	*iso*Butyl	672 or 708	668 or 708
n-Propyl	553	652	*tert.*-Butyl	587	587
*iso*Propyl	630	626			

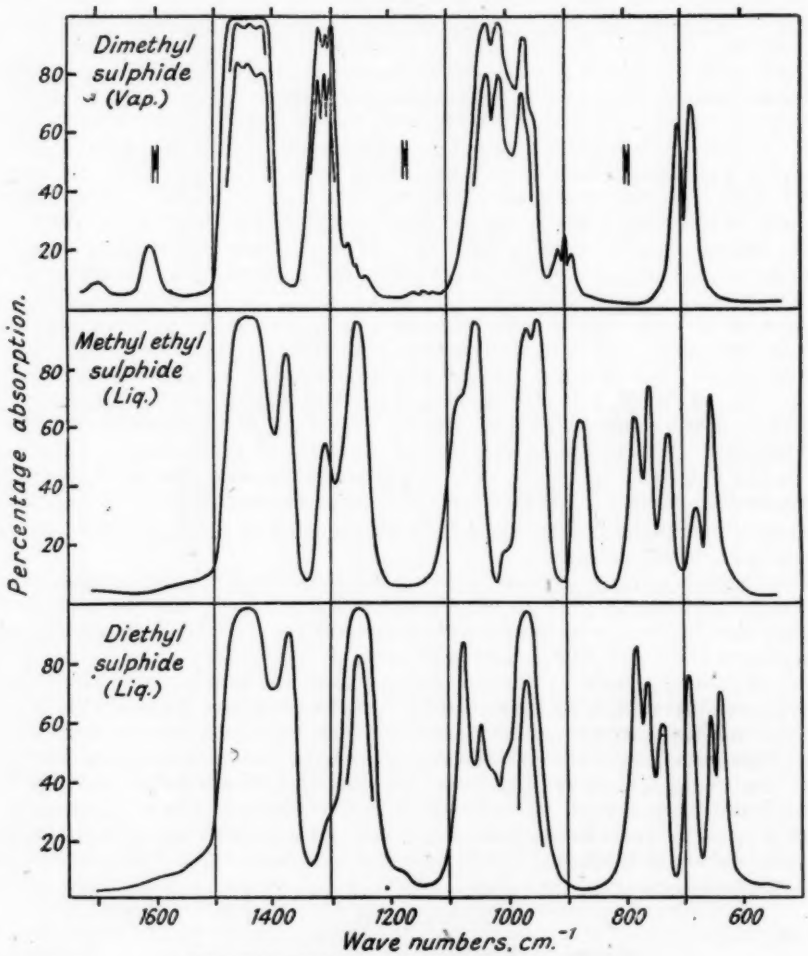
Whatever the correct assignment may be in this case, it is clear that whilst the C–S stretching frequency lies in the region of 600—700 cm.$^{-1}$, it varies appreciably in different cases. If it is to be used in diagnosis with such structures as vulcanised rubber, the identification will have to be made with caution.

(2) *Alkyl Sulphides.*—The spectra of three alkyl sulphides are shown in Fig. 4. Although the results for dimethyl sulphide do not disagree with those given previously (*Trans. Faraday Soc.*, 1941, **37**, 1), some of the bands are now much better resolved. Thus the shoulders previously found at 917 and 976 cm.$^{-1}$ now appear as definite bands at 900 and 970 cm.$^{-1}$, and the band at 1310 has a clear three-branch contour. There seem to be three types of band contour, corresponding in principle to *A*, *B*, and *C* type bands. Although the present measurements do not directly invalidate any of the previous tentative assignments, some apparent discrepancies with the Raman data probably require further examination. There is little doubt that the

infra-red band at about 694 cm.$^{-1}$ is connected with the symmetrical stretching mode of the C–S–C skeleton. The corresponding C–S–C antisymmetrical mode has a frequency 742 found as a depolarised Raman interval.

The Raman spectra of diethyl and methyl ethyl sulphides have been measured by Matossi and Aderhold (*Z. Physik*, 1931, **68**, 683) and by Venkateswaran (*Indian J. Physics*, 1931, **6**, 51), and the intervals found agree well with the positions of many of the infra-red bands. With these compounds some changes of relative intensity of certain bands occur on passing from the vapour to the liquid, and in several cases there is a small but definite change in the frequency of the band. There is little doubt that the vibrations mainly determined by stretching of the C–S bonds give rise to bands in the region 600—750 cm.$^{-1}$, and while it is impossible to make a definite assignment, it seems probable that the " symmetrical " C–S–C stretching frequency lies at

FIG. 4.



Dimethyl sulphide, 27 cm. path, 100—250 mm.
Liquids, approx. 0·1 mm. layer.

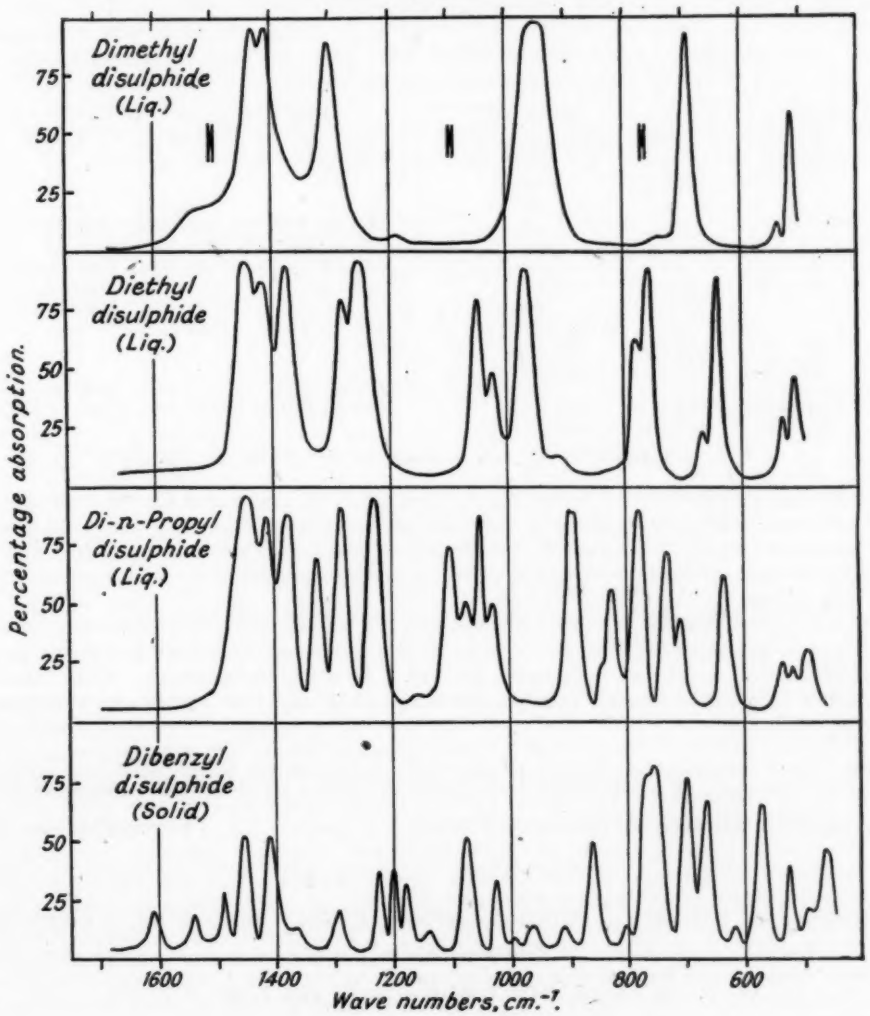
652 cm.$^{-1}$ with methyl ethyl sulphide and at 640 cm.$^{-1}$ with the diethyl derivative, corresponding to 694 with dimethyl sulphide. In ethylene disulphide (Thompson and Dupré, *Trans. Faraday Soc.*, 1940, **36**, 805) this mode has a value of 625 cm.$^{-1}$.

Another point of interest is the frequency of the symmetrical deformation mode of the CH_3 groups. This is usually found near 1375 cm.$^{-1}$ in hydrocarbons. In methyl ethyl and diethyl sulphides there is a band at about this value, but in dimethyl sulphide where the methyl groups are attached to sulphur instead of carbon, the band is displaced. Originally, the band at 1310 with dimethyl sulphide was attributed to the deformation of the methyl group. The bands at about 1450—1460 cm.$^{-1}$ with all the compounds are connected with other deformations of C–H links.

(3) *Alkyl and Aryl Disulphides.*—The spectra of dimethyl, diethyl, di-*n*-propyl, and dibenzyl sulphides are shown in Fig. 5. The Raman spectra of the first two have been recorded by Venkateswaran (*Indian J. Physics*, 1931, **6**, 51), by Venkateswaran and Paridga (*J. Indian Acad. Sci.*, 1942, *A*, **15**, 396) and by Douzelait and Chaix (*Compt. rend.*, 1936, **202**, 851). A recent paper by Gerding and Westrick (*Rec. Trav. chim.*, 1942,

61, 412) is not yet obtainable. The results are collated with the present infra-red data in Tables III and IV. Only frequencies below 1500 cm.$^{-1}$ are included since the only fundamentals above this value will be due to C–H stretching vibrations near 2900 cm.$^{-1}$. Stevenson and Beach (*J. Amer. Chem. Soc.*, 1938, **60**, 2872) have determined the structural parameters of dimethyl disulphide by electron diffraction. Their results suggest a non-linear arrangement of the skeleton C–S–S–C. If rotation about the S–S bond is restricted, *cis-* and *trans*-forms may therefore exist. In this event, the *trans*-form may have a centre of symmetry, and if only the *trans*-form were present no coincidences should be found between the Raman and the infra-red

FIG. 5.



Liquids in about 0·1 mm. layer.

fundamentals. Coincidences certainly occur, as shown in Table III. Hence the sample examined cannot be solely *trans-* in structure. On the other hand, molecular distortions in the liquid might lead to violation of the normal selection rules.

TABLE III.

Dimethyl Disulphide.

Raman.	Infra-red.	Raman.	Infra-red.
243 (1d)	—	948 (1)	950 (s.)
284 (0d)	—	—	1192 (v.w.)
512 (6s)	517 (m.)	1305 (0)	1298 (s.)
—	533 (v.w.)	1337 (0)	—
695 (6s)	690 (s.)	—	1410 (s.)
740 (0d)	741 (?)	1425 (0d)	1432 (s.)

It seems likely that the infra-red band at 690 cm.$^{-1}$ is connected with the stretching of C–S bonds, and that at 517 may be associated with the stretching of S–S links. The vibration frequency of chlorine is 536 cm.$^{-1}$, and according to Raman measurements by Venkateswaran on liquid sulphur (*Proc. Indian Acad. Sci.*, 1936, *A*, **4**, 34) an interval of 470 cm.$^{-1}$ is attributed to the S–S stretching mode. Morino and Mizushima (*Sci. Papers Inst. Res. Tokyo*, 1937, **32**, 220) also attribute a Raman interval of 536 in disulphur dichloride to the S–S stretching vibration.

As in the case of dimethyl sulphide (above), the symmetrical deformation frequency of the methyl groups, usually found near 1375 cm.$^{-1}$, is displaced in dimethyl disulphide, whereas with the diethyl and the dipropyl derivative, in which methyl groups are attached directly to carbon, a band appears at 1375.

The Raman and infra-red results with diethyl disulphide show good concordance.

TABLE IV.

Diethyl Disulphide.

Raman intervals, cm.$^{-1}$.*			Infra-red	Raman intervals, cm.$^{-1}$.*			Infra-red
V. (1942).	V. (1931).	D. (1936).	bands, cm.$^{-1}$.	V. (1942).	V. (1931).	D. (1936).	bands, cm.$^{-1}$.
115 (4) D	—	—	—	756 (2) P	764 (0d)	—	758 (s.)
189 (7) 0·71	—	179 (w.)	—	—	—	—	778 (s.)
197 (3) 0·80	—	—	—	—	—	—	925 (v.w.)
259 (1d) D	—	—	—	969 4b) 0·79	967 (4d)	964 (w.)	966 (v.s.)
295 (1d) D	—	—	—	1033 (2) D	1033 (0)	—	1025 (m.)
324 (1d) 0·60	333 (0)	—	—	1052 (5) 0·45	1052 (4)	1045 (v.w.)	1049 (s.)
357 (2d) D	384 (0)	—	—	1125 (1) D	—	1142 (w.)	—
400 (1) D	—	—	—	—	—	1187 (w.)	—
458 (1) P	—	—	—	1257 (3) 0·57	1260 (1b)	—	1255 (s.)
506 (7) 0·32	509 (6)	507 (w.)	509 (w.)	1294 (1)	—	—	1280 (s.)
520 (4) 0·25	525 (3)	522 (w.)	527 (v.w.)	—	—	—	1375 (s.)
578 (1)	—	—	—	1417 (3) 0·84	1422 (2)	1420 (w.)	1416 (m.)
648 (10) 0·57	641 (8)	639 (s.)	642 (m.)	1444 (3) 0·86	1454 (2d)	1446 (w.)	1445 (v.s.)
668 (5) 0·48	667 (4)	663 (w.)	668 (v.w.)				

* V. = Venkateswaran; D. = Douzelait and Chaix (*loc. cit.*).

The array of plausible fundamentals seems larger than could be accounted for by a single *cis*- or *trans*-structure. The infra-red bands at 642 and 509 cm.$^{-1}$ are probably connected with the stretching of C–S and S–S bonds, but the other frequencies cannot be definitely assigned. It is noteworthy that many of the infra-red bands (and also Raman intervals) are accompanied by satellites, which may be connected with the existence of *cis*- and *trans*-forms.

No Raman data are available for the other disulphides. With the di-*n*-propyl derivative there is a band at 631 cm.$^{-1}$ which may be connected with the stretching of a C–S bond, and there is a feeble group of bands near 500 cm.$^{-1}$ which may be connected with motions of the S–S part of the skeleton. With dibenzyl sulphide many of the infra-red bands are common to aromatic compounds, and that at 570 cm.$^{-1}$ may be associated with stretching of C–S bonds.

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THE PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, December 6th*, 1945.]

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95. *Some Derivatives of Simple Carbohydrates Containing Unsaturated Substituents.**

By W. N. HAWORTH, (MRS.) H. GREGORY, and L. F. WIGGINS.

In this paper several acrylates and methacrylates of simple six-carbon chain carbohydrates are described and are shown to polymerise very readily to give transparent colourless resins of the thermosetting type. Acetal derivatives from hexahydric alcohols with unsaturated aldehydes, and a diallyl ester of a saccharic acid derivative have also been prepared but none of these undergoes polymerisation.

LITTLE success seems to have attended earlier endeavours to utilise carbohydrates as constituents of synthetic resins, and few appropriate derivatives of carbohydrates are known which can undergo polymerisation readily. Cellulose, starch, and sucrose, because of their great abundance, would appear to provide opportunities for this kind of investigation. Sucrose is the chief source of the initial material employed in this investigation; it is readily hydrogenated to give high yields of sorbitol and mannitol.

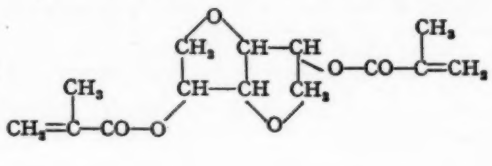
We have found that 1 : 6-diamino 2 : 4-3 : 5-dimethylene mannitol (Haworth, Heath, and Wiggins, *J.*, 1944, 155) and 2 : 4-3 : 5-dimethylene gluco- and *l*-ido-saccharic acids (Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61), when appropriately mixed together or with other dibasic acids or diamines respectively, gave polyamides which were not sufficiently thermostable to compare with products of the Nylon type. In addition,

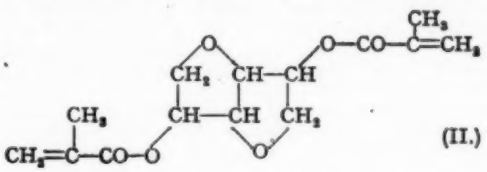
* Patent applied for.

sorbitol and mannitol partly substituted with formaldehyde residues, *e.g.*, 2 : 4-3 : 5-dimethylene sorbitol and mannitol (Haworth and Wiggins, *J.*, 1944, 58), were obtained with the object of forming polyesters with suitable dibasic acids, but again no useful products were obtained.

In the work herein reported we have sought to introduce unsaturated acyl groups into the sugar or polyhydric alcohol derivative, and have used acrylyl and methacrylyl * residues and have obtained polyacrylyl or methacrylyl sugar or sugar alcohol derivatives. As suitable compounds derived from sugar alcohols we investigated the dianhydrides of sorbitol and mannitol and the dimethylene and dibenzylidene derivatives of the hexahydric alcohols. Methods for preparing dianhydro mannitol and sorbitol have been described and their constitutions, as 1 : 4-3 : 6-dianhydrides of the hexitols, were determined by Wiggins (*J.*, 1945, 4) and Montgomery and Wiggins (this vol., p. 390). Since these substances were shown to have extremely stable structures they appear to be admirably suited for the purpose in view. On treating each substance, dissolved in sodium hydroxide solution, with *methacrylyl chloride* the 2 : 5-dimethacrylyl derivatives were precipitated. The derivative of the anhydride of mannitol, *i.e.* 2 : 5-*dimethacrylyl* 1 : 4-3 : 6-*dianhydro mannitol* (I), was obtained in crystalline form, whereas 2 : 5-*dimethacrylyl* 1 : 4-3 : 6-*dianhydro sorbitol* (II) was a liquid. Both compounds, however, were found to polymerise easily, and furnished hard, colourless, infusible and insoluble resins. The polymerisation was simply effected by heating the substances for a few minutes at 80°

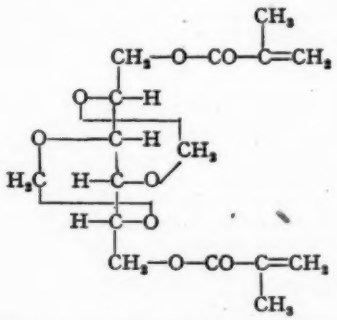
(I.)

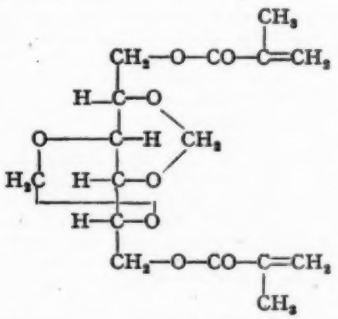




(II.)

(III.)





(IV.)

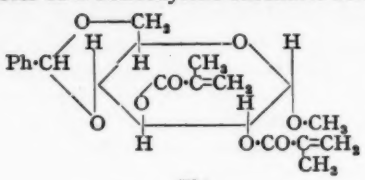
without the addition of peroxides. Apparently homogeneous co-polymers could also be formed by heating with methyl methacrylate in the presence of benzoyl peroxide. The effect of the added methacrylyl derivative of dianhydro hexitol was to harden methyl methacrylate polymers and to increase the rate of polymerisation. The methacrylate could also be made in pyridine solution if methacrylic anhydride (prepared according to U.S.P. 2,143,924, 1939) was used as the acylating agent, although by this method the yields were generally slightly lower. 2 : 5-Diacrylyl 1 : 4-3 : 6-dianhydro sorbitol was also obtained in crystalline form using sodium hydroxide and acrylyl chloride [prepared by Kohler's modification (*Amer. Chem. J.*, 1909, **42**, 380) of Moureu's method (*Ann. Chim. Phys.*, 1894, **2**, 161)]. This sorbitol derivative polymerised at 80° but the rate of polymerisation was rather slower than in the case of the corresponding methacrylyl derivative.

For effecting acrylylation and methacrylylation of derivatives of mannitol and sorbitol themselves the most useful starting materials were those in which the four central hydroxyl groups of the hexitol were substituted in acetal formation with formaldehyde. Other aldehydes might also be used but the formaldehyde compounds were found to be the most stable. Thus 1 : 6-*dimethacrylyl* 2 : 4-3 : 5-*dimethylene mannitol* (III), 1 : 6-*diacrylyl* 2 : 4-3 : 5-*dimethylene mannitol*, and 1 : 6-*dimethacrylyl* 2 : 4-3 : 5-*dimethylene sorbitol* (IV) were obtained, all in crystalline form. Similarly from a *dibenzylidene sorbitol* (prepared by debenzoylation of the 1 : 6-dibenzoyl dibenzylidene sorbitol of Vargha, *Ber.*, 1935, **68**, 1377) 1 : 6-*dimethacrylyl* 2 : 3 : 4 : 5-*dibenzylidene sorbitol* was obtained. All these compounds on being heated just above their melting points polymerised extremely easily without the use of catalysts to form hard, transparent, infusible, insoluble resins. One sugar derivative, namely 4 : 6-benzylidene α-methylglucoside, has been subjected to methacrylylation and crystalline 2 : 3-dimethacrylyl 4 : 6-benzylidene α-methylglucoside (V) obtained. This substance rapidly polymerised when heated above its melting point.

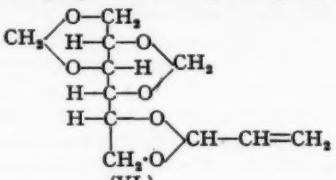
Acetal derivatives of mannitol and sorbitol have also been made with aldehydes containing unsaturated linkages in the anticipation that these might polymerise. For this purpose acraldehyde and cinnamaldehyde were used. 1 : 3-2 : 4-Dimethylene sorbitol (Bourne and Wiggins, *J.*, 1944, 517) was treated with acraldehyde in the presence of zinc chloride and a small yield of 1 : 3-2 : 4-*dimethylene* 5 : 6-*acrylidene sorbitol* (VI) was obtained.

* Since this work was completed, Treadway and Yanovsky (*J. Amer. Chem. Soc.*, 1945, **67**, 1038) have reported the preparation of the methacrylates of glucose, dextrin, and starch.

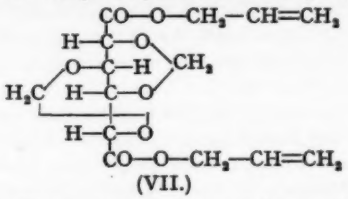
Again, mannitol on treatment with cinnamaldehyde gave *tricinnamylidene mannitol*. Finally an unsaturated ester of a dimethylene saccharic acid was prepared, namely *diallyl* 2 : 4-3 : 5-*dimethylene glucosaccharate* (VII).



(V.)



(VI.)



(VII.)

None of these substances, however, showed any tendency to polymerise in the presence of benzoyl peroxide as catalyst.

Experimental.

Methacrylyl Chloride.—To dry potassium methacrylate (62 g.), prepared by hydrolysis of methyl methacrylate by aqueous-alcoholic potash, phosphorus oxychloride (38 g.) was slowly added, with good stirring (compare Moureu (*loc. cit.*)). After the addition the mixture was heated on a boiling water-bath for 1 hour and thereafter the product was distilled on an oil-bath. The crude product was purified by twice distilling over dry potassium methacrylate (1—2 g. portions). *Methacrylyl chloride* had b. p. 95° and was obtained in 64·0% yield as an extremely lachrymatory mobile liquid (Found : C, 45·8; H, 4·9; Cl, 33·3. C_4H_5OCl requires C, 45·9; H, 4·8; Cl, 33·9%).

Methacrylic Anhydride.—This was obtained according to the procedure given by Rubenstein in U.S.P. 2,143,924 (1939) in 80% yield. The only modification employed was in the use of potassium methacrylate instead of the sodium salt.

Acrylyl Chloride.—This was prepared from sodium acrylate (70 g.) and phosphorus oxychloride (33·6 c.c.) by Moureu's method (as modified by Kohler, *loc. cit.*). The yield was 60% of the theoretical and the product boiled at 76—77° after purification by distillation over anhydrous sodium acrylate.

2 : 5-*Dimethacrylyl* 1 : 4-3 : 6-*Dianhydro Mannitol.*—(*a*) Dianhydro mannitol (4·0 g.) was dissolved in sodium hydroxide (5N, 20 c.c.) and methacrylyl chloride carefully added at 0° with vigorous shaking. The crystalline *product* which rapidly separated was collected, washed with water, and dried in a vacuum. It recrystallised from ligroin (b. p. 100—120°) in colourless flakes (yield, 2·6 g.; 33% of the theoretical), m. p. 67°, $[\alpha]_D$ + 176·6° in chloroform (*c*, 0·586) (Found : C, 59·7; H, 6·4. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%).

Some loss in yield is accounted for by the fact that polymerisation occurs during the initial reaction and during the recrystallisation of the product, since about 15% of the crude product remains insoluble in ligroin.

(*b*) To a solution of dianhydro mannitol (2·0 g.) in dry pyridine (10 c.c.) was added methacrylic anhydride (8·4 g.). After keeping for 24 hours at room temperature the mixture was poured into ice-water, and the crystalline product was filtered off, washed with water, dried in a vacuum, and recrystallised from ligroin (b. p. 100—120°) (yield, 1·1 g.; 28% of the theoretical). It had m. p. 67°, and was identical with the material obtained above.

When 2 : 5-dimethacrylyl 1 : 4-3 : 6-dianhydro mannitol was heated above its m. p. (*i.e.*, at 80°) for only a few minutes, without the addition of benzoyl peroxide, polymerisation took place and a hard colourless transparent resin was obtained. Polymerisation also took place when the substance was heated with twice its weight of methyl methacrylate, but here benzoyl peroxide was necessary. After 1½ hours' heating at 100° an apparently homogeneous hard colourless resin was obtained.

2 : 5-*Dimethacrylyl* 1 : 4-3 : 6-*Dianhydro Sorbitol.*—Dianhydro sorbitol (5 g.) was dissolved in sodium hydroxide (5N, 20 c.c.), cooled to 0° and methacrylyl chloride added slowly. After being shaken for a few minutes, the reaction mixture was exhaustively extracted with ether, the ether extract dried ($MgSO_4$), and the ether removed. A thin colourless liquid remained which failed to crystallise (yield, 4 g.; 41% of the theoretical), $[\alpha]_D$ + 78·2° in chloroform (*c*, 1·74) (Found : C, 59·5; H, 6·4. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). Distillation under reduced pressure over quinol at 190° (bath temperature) could only be accomplished with large losses. The sorbitol compound polymerised to a hard colourless resin on keeping at room temperature for three days. It also polymerised very rapidly when heated on a boiling water-bath, but the product was a gel which did not harden on prolonged heating. Similarly polymerisation in toluene solution took place with precipitation of a gelatinous polymer, without there being any obvious increase in the viscosity of the solution. When 2 parts of the liquid dimethacrylyl dianhydro sorbitol were dissolved in 3 parts of methyl methacrylate and the solution heated at 100° for 15 minutes in the presence of benzoyl peroxide a hard infusible glass was obtained. All these resins were insoluble in organic solvents.

2 : 5-*Diacrylyl Dianhydro Sorbitol.*—Dianhydro sorbitol (2 g.) was dissolved in sodium hydroxide solution (5N, 20 c.c.), cooled in ice, and acrylyl chloride added slowly with shaking. The oily layer which rapidly separated was extracted with ether, the ether extract dried ($MgSO_4$), and the ether removed leaving a crystalline residue. After being recrystallised from ligroin (b. p. 100—120°) shining flakes of 2 : 5-*diacrylyl dianhydro sorbitol* were obtained (yield, 0·9 g.; 26% of the theoretical), m. p. 57°, $[\alpha]_D$ + 130·9° in chloroform (*c*, 1·054) (Found : C, 56·8; H, 5·5. $C_{12}H_{14}O_6$ requires C, 56·6; H, 5·6%).

This substance polymerised to a hard transparent colourless resin when heated for 40 minutes on a boiling water-bath. Copolymerisation with an equal weight of methyl methacrylate to a hard durable resin took place in the presence of benzoyl peroxide within 2½ hours at 100°.

1 : 6-*Dimethacrylyl* 2 : 4-3 : 5-*Dimethylene Sorbitol.*—Dimethylene sorbitol (0·4 g.) prepared by the method of Haworth and Wiggins (*loc. cit.*) was dissolved in sodium hydroxide solution (10 c.c. of 5N) and a slight excess of methacrylyl chloride (0·5 g.) added at 0° with vigorous shaking. Colourless crystals rapidly separated, and were collected and recrystallised from ethyl alcohol from which the *compound* was obtained in fine needles, m. p. 90°, $[\alpha]_D^{18°}$ + 93·2° in chloroform (*c*, 2·236) (Found : C, 55·8; H, 6·6. $C_{16}H_{22}O_8$ requires C, 56·1; H, 6·5%).

This substance polymerised on heating for a few minutes above its m. p. to a hard colourless resin.

1 : 6-*Dimethacrylyl* 2 : 4-3 : 5-*Dimethylene Mannitol.*—(*a*) Dimethylene mannitol (4 g.) was treated with methacrylyl chloride (4·5 g.) in sodium hydroxide solution (5N, 20 c.c.) as in the previous preparation. The *product*, recrystallised from ligroin (b. p. 100—120°), formed prismatic crystals (yield, 4·3 g.; 65% of the theoretical), m. p. 85°, $[\alpha]_D^{18°}$ + 88·7° in chloroform (*c*, 1·065) (Found : C, 56·1; H, 6·3. $C_{16}H_{22}O_8$ requires C, 56·1; H, 6·5%).

(*b*) Dimethylene mannitol (2 g.) dissolved in dry pyridine (40 c.c.) was treated with methacrylic anhydride (6 g.; 100% excess) and the mixture set aside for 24 hours at room temperature. On pouring into water a solid product separated which recrystallised from ligroin (b. p. 100—120°) and was identical with the 1 : 6-dimethacrylyl 2 : 4-3 : 5-dimethylene mannitol obtained above.

During the recrystallisation of the crude material from these experiments an insoluble solid was always obtained which could not be melted and was doubtless polymerised material (Found: C, 56·4; H, 6·5. $(C_{16}H_{22}O_8)_n$ requires C, 56·1; H, 6·5%). Dimethacrylyl dimethylene mannitol polymerised extremely quickly on heating above its m. p. After 2 minutes' heating at 90° the melt sets to a hard, transparent, infusible resin. In appearance the resin resembles polymerised methyl methacrylate but it is much harder and quite insoluble in organic solvents. It was only decomposed slowly on boiling with concentrated mineral acid. Apparently no polymerisation occurred on heating the monomer in toluene solution until the toluene had been removed by evaporation. Homogeneous co-polymerisation occurred with an equal weight of methyl methacrylate in the presence of benzoyl peroxide. The product, a hard infusible glass, was insoluble in all solvents.

1 : 6-*Diacrylyl* 2 : 4-3 : 5-*Dimethylene Mannitol.*—To a solution of 2 : 4-3 : 5-dimethylene mannitol in 5N-sodium hydroxide (20 c.c.) cooled to 0° there was added, slowly and with vigorous shaking, acrylyl chloride (2 g.). A thick oily liquid separated which slowly solidified. Recrystallisation from ligroin (b. p. 100—120°) gave 1 : 6-*diacrylyl dimethylene mannitol* (1·1 g.; 36·4% of the theoretical), m. p. 86°, $[\alpha]_D^{18°}$ + 89·8° in chloroform (*c*, 0·512) (Found: C, 53·4; H, 5·8. $C_{14}H_{18}O_8$ requires C, 53·4; H, 5·8%). The pure product polymerised on heating just above its m. p. to form first a soft gel, then a brittle transparent gel. The polymerisation was complete in 10 minutes without the addition of a catalyst. When an equal weight of methyl methacrylate was added to the diacrylyl dimethylene mannitol and the mixture heated on the boiling water-bath in a sealed tube in the presence of benzoyl peroxide a polymer was obtained which did not appear to be homogeneous.

2 : 4-3 : 5-*Dibenzylidene Sorbitol.*—1 : 6-Dibenzoyl dibenzylidene sorbitol (v. Vargha, *loc. cit.*) (5 g.) (m. p. 208°) was shaken overnight with dry methyl alcohol containing sodium (50 mg.). Complete solution occurred and on evaporation under reduced pressure a solid *product* was obtained which after recrystallisation from acetone–ligroin had m. p. 208° (the m. p. was depressed in admixture with starting material), $[\alpha]_D$ − 14·8° in acetone (*c*, 0·945). Yield, 2·8 g. (Found: C, 66·6; H, 6·2. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·1%).

1 : 6-*Dimethacrylyl* 2 : 3 : 4 : 5-*Dibenzylidene Sorbitol.*—2 : 3 : 4 : 5-Dibenzylidene sorbitol (2 g.) was dissolved in dry pyridine (40 c.c.) and methacrylic anhydride (3·5 g.) added. The mixture was kept at room temperature for 24 hours. On pouring into ice-water a precipitate was obtained which was collected and recrystallised from ligroin (b. p. 100—120°). The product, 1 : 6-*dimethacrylyl* 2 : 3 : 4 : 5-*dibenzylidene sorbitol*, had m. p. 135° and $[\alpha]_D^{18°}$ − 26·2° in chloroform (*c*, 0·535) (Found: C, 68·2; H, 6·1. $C_{28}H_{30}O_8$ requires C, 68·0; H, 6·1%).

On heating to 150° the crystals melted and rapidly polymerised to a hard insoluble resin.

2 : 3-*Dimethacrylyl* 4 : 6-*Benzylidene α-Methylglucoside.*—4 : 6-Benzylidene α-methylglucoside (2 g.), dissolved in dry pyridine, was treated with methacrylic anhydride (4·4 g.) and the mixture set aside for 24 hours. Thereafter it was poured into ice-water, and the precipitate was collected, washed with water, dried, and recrystallised from ligroin. The *compound* had m. p. 181°, $[\alpha]_D^{18°}$ + 90·4° in chloroform (*c*, 0·509) (Found: C, 62·8; H, 6·4. $C_{22}H_{26}O_8$ requires C, 63·1; H, 6·3%). Polymerisation occurred as soon as the compound melted, yielding a hard, transparent glass. The methacrylyl residues in this substance could be removed by treatment with alcoholic sodium methoxide at room temperature, the original 4 : 6-benzylidene α-methylglucoside being isolated.

1 : 3-2 : 4-*Dimethylene* 5 : 6-*Acrylidene Sorbitol.*—A mixture of dimethylene sorbitol (1·5 g.) (Bourne and Wiggins, *loc. cit.*), zinc chloride (1·5 g.), and acraldehyde (20 c.c.) was shaken for 5 hours. The solution obtained was poured into a ligroin–water mixture and a solid *product* separated. This was recrystallised several times from ethyl alcohol (yield, 0·6 g.; 32% of the theoretical), m. p. 160, $[\alpha]_D^{18°}$ + 280·5° in chloroform (*c*, 0·82) (Found: C, 54·5; H, 6·6. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%).

Attempts to polymerise this substance with or without benzoyl peroxide were unsuccessful.

Tricinnamylidene Mannitol.—Mannitol (5 g.), zinc chloride (5 g.), and cinnamaldehyde (30 c.c.) were shaken together for 3 days, and the resulting solution poured into a water–ligroin mixture. The syrup which separated was washed with water and triturated with alcohol; crystallisation then took place. On being recrystallised from alcohol *tricinnamylidene mannitol* separated in fine needles, m. p. 209°. Yield, 1·6 g.; 12% of the theoretical, $[\alpha]_D^{18°}$ − 36·3° in chloroform (*c*, 1·048) (Found: C, 75·3; H, 6·0. $C_{33}H_{32}O_6$ requires C, 75·5; H, 6·1%).

Attempts to polymerise this substance by heating in a sealed tube at 235° in the presence of benzoyl peroxide failed.

Diallyl 2 : 4-3 : 5-*Dimethylene Glucosaccharate.*—A solution of dimethylene glucosaccharic acid (1 g.) (Haworth, Jones, Stacey, and Wiggins, *loc. cit.*) in 1% allyl alcoholic hydrogen chloride (5 c.c.) was boiled for 6 hours. Thereafter it was neutralised with silver carbonate, the solution filtered, the residue washed with acetone, and the combined filtrates decolourised with animal charcoal and evaporated to dryness. The syrup obtained crystallised on trituration with alcohol. After being recrystallised from ether–ligroin the *diallyl* ester of 2 : 4-3 : 5-dimethylene glucosaccharic acid separated in fine needles. Yield, 0·75 g., m. p. 60°, $[\alpha]_D$ + 65·0 in chloroform (*c*, 0·40) (Found: C, 53·9; H, 6·0. $C_{14}H_{18}O_8$ requires C, 53·5; H, 5·8%).

This product could not be polymerised on heating at 100° for 12 hours.

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96. *Synthesis of Sulphanilylguanidine.*

By S. BIRTWELL, E. HAWORTH, F. L. ROSE, G. SWAIN, and C. H. VASEY.

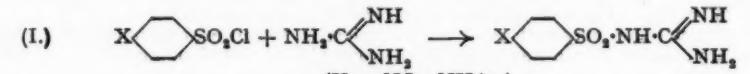
The synthesis of sulphanilylguanidine by four different reactions is described: (*a*) From *p*-acetamidobenzenesulphonamide and dicyandiamide; (*b*) from *p*-acetamidobenzenesulphonyl-*S*-methyl*iso*thiourea by amidation, and hydrolysis at the acetamido group of the reaction product; (*c*) from sulphanilamide and *S*-methyl*iso*thiourea, or other related *iso*thioureas; (*d*) from sulphanilamide and guanidine.

p-AMINOBENZENESULPHONYLGUANIDINE (sulphanilylguanidine, sulphaguanidine) has attained importance as a chemotherapeutic agent, useful for treatment of certain pathogenic intestinal infections (Marshall *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163; 1941, **68**, 94; *Brit. Med. J.*, 1941, 497, 514; *J. Amer. Med. Assoc.*, 1941, **117**, 326; Frisk, *Acta med. scand.*, 1941, **109**, 355). It was also required by us for the manufacture of the sulphanilamide derivative of 2-amino-4 : 6-dimethylpyrimidine (Rose and Swain, *J.*, in press). Its synthesis

has in consequence been extensively investigated in these laboratories during 1941—1942. Earlier publication has not been possible owing to war circumstances. Several routes have been examined in detail and we record here the main conclusions drawn from our researches.

Sulphanilylguanidine was first prepared in 1938 by Buttle and co-workers (*Biochem. J.*, 1938, **32**, 1101) by the interaction of dicyandiamide and sulphanilamide, but was mistakenly given the constitution 4-guanidinobenzenesulphonamide. Its true structure was revealed after the same substance had been prepared by Roblin *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2002) by the action of *p*-nitrobenzenesulphonyl chloride (I, X = NO_2) on guanidine, followed by reduction, and later analogously by Marshall *et al.* (*loc. cit.*) from *p*-acetamidobenzenesulphonyl chloride (I, X = NHAc) followed by hydrolysis at the acetamido group:

(A)

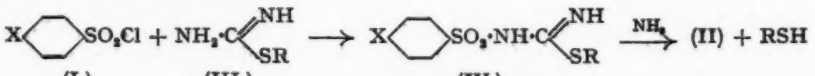


(I.) (II.)

(X = NO_2, NHAc.)

In addition to an examination of the above methods of synthesis, others, derived from existing reactions employed for guanidines in general, have been investigated as follows:

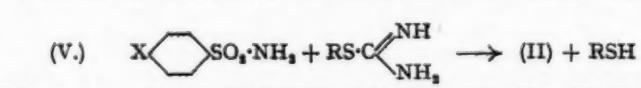
(B) Formation of a suitable benzenesulphonyl*iso*thiourea and conversion into the corresponding guanidine by ammonia with elimination of a thiol:



(I.) (III.) (IV.)

(X = NO_2, NHAc; R = Me, Et, Ph·CH_2.)

(C) Interaction of a suitably *p*-substituted benzenesulphonamide and an *iso*thiourea with elimination of a thiol:



(V.) (II.)

(X = NO_2, NH_2, NHAc; R = Me, Et, $CH_2{:}CH{\cdot}CH_2$, $HO[CH_2]_2$, $HO[CH_2]_3$, $[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, C_6H_{11}, Ph·CH_2.)

(D) Interaction of sulphanilamide and guanidine with elimination of ammonia:

(British Spec. No. 571,780, describing a similar method of preparation, appeared whilst this paper was in preparation for press.)

Reaction (A) was repeated with both *p*-acetamido- and *p*-nitro-benzenesulphonyl chloride; the former was found to give the higher yield (55%) at the condensation stage, which was carried out in aqueous acetone, or *iso*propyl alcohol in the presence of sodium hydroxide. Hydrolysis of the acetamido group with dilute hydrochloric acid effected conversion into sulphanilylguanidine in 80—90% yield.

Reaction (B): The highest yields of (IV, X = NHAc, R = Me) (77%) were obtained in the first stage of the interaction with (I, X = NHAc) and (III, R = Me). Although the amidation took place in the absence of a solvent at high temperatures, a much more satisfactory conversion into the guanidine (II, X = NHAc) occurred at 110° by passing ammonia into a phenol solution of the *iso*thiourea (IV). Other substituents (R = Et, Ph·CH_2; X = NHAc) gave lower yields.

Reaction (C): Although it is well known that alkyl guanidines can be made by treating a primary or secondary alkylamine with *S*-methyl*iso*thiourea sulphate with elimination of methylthiol, a similar reaction with a sulphonamido group, especially in the presence of a primary amino group in the same molecule, was not to be expected. However, we have found that such a reaction does take place under carefully controlled conditions. Thus when several *iso*thiourea salts were caused to react with the sodium salt of the sulphonamides (V), or with the free sulphonamides in the presence of an equivalent of alkali, the corresponding guanidines were formed and a thiol eliminated. *S*-Methyl*iso*thiourea sulphate was found to be the most suitable of the *iso*thiourea salts examined.

Reaction conditions have been most extensively examined where the reactants were sulphanilamide and *S*-methyl*iso*thiourea sulphate. Phenol was selected as solvent since it dissolves the sodio-sulphanilamide readily.

Optimum reaction temperature was 150—180°; below this range the yield fell rapidly. The sodio-sulphanilamide was either preformed or made *in situ* in phenol by adding sodium hydroxide or sodium carbonate. Various inorganic and organic bases were also used in the reaction. The order and method of mixing the reactants had a marked influence upon the yield. Continuous and smooth addition of the methyl*iso*thiourea sulphate during 3 hours to a solution of sodio-sulphanilamide in phenol at 160° gave the best yields. Rapid addition gave a diminished yield (5—7%), and addition over a period greater than 3 hours also decreased the yield. The actual course of the reaction has not been determined, but it is suggested that the free *iso*thiourea was first formed. This may then have reacted in one of two ways:

(1) Directly with the sulphonamide group as in C above.

(2) Through initial decomposition to cyanamide which then reacts with the sulphonamide group. A similar mechanism has been discussed for the synthesis of alkylated guanidines from alkylated *iso*thioureas and dialkylamines (cf. Schotte, Priewe, and Roescheisen, *Z. physiol. Chem.*, 1928, **174**, 119; Lecher, *ibid.*, 1928, **176**, 43). In this event the cyanamide would undoubtedly also tend to polymerise, and it may be significant that minimal concentrations of *iso*thiourea and maximal concentrations of sulphanilamide have been shown to influence the reaction in favour of sulphanilylguanidine formation. Against this it was observed that cyanamide itself, when fused with sulphanilamide, gave only a 14% yield of sulphanilylguanidine, whilst other substances capable of liberating cyanamide on heating gave even lower yields.

Reaction (D) : Decomposition of the guanidine salt of sulphanilamide afforded the most facile method for the preparation of sulphanilylguanidine. α-Methyl- and αα-dimethyl-guanidine by a similar reaction yielded mainly sulphanilylguanidine, but α-phenylguanidine gave sulphanilylguanidine only as a by-product, with β-sulphanilyl-α-phenylguanidine as the main product.

Experimental.

(All melting points uncorrected.)

Reaction between p-*Acetamidobenzenesulphonamide and Dicyandiamide.*—*p*-Acetamidobenzenesulphonamide (53·5 g., 0·8 mol.) and dicyandiamide (26·3 g., 1 mol.) were intimately mixed by grinding and the mixture stirred and heated to 200° in an oil-bath until a vigorous reaction set in (15 minutes). When the initial reaction had subsided heating was continued for 1 hour. The product was cooled to 70° and digested with a solution of sodium hydroxide (11·5 g. in 20 c.c. of water), cooled rapidly to below 15° by addition of ice, and allowed to stand for 3 hours. The crude *p*-acetamidobenzenesulphonylguanidine was filtered, resuspended in cold water (100 c.c.), and again filtered and washed with cold water. Yield 22·0 g., m. p. 240°. Recrystallisation from hot water with charcoal treatment gave colourless crystalline *p*-acetamidobenzenesulphonylguanidine (19·8 g.; 36%), m. p. 254—255° (Marshall *et al.*, *loc. cit.*, give m. p. 264·5—267·5°, softens at 261°). A repetition of the method of Buttle *et al.* (*loc. cit.*) employing sulphanilamide and dicyandiamide gave a 5—10% yield of sulphanilylguanidine, m. p. 183—185° (Roblin *et al.*, *loc. cit.*, give m. p. 189—190°).

Reaction B. p-*Acetamidobenzenesulphonyl*-S-*methylisothiourea* (IV, X = NHAc, R = Me).—The method of preparation described by Cox (*J. Org. Chem.*, 1942, **7**, 307) was employed with slight modifications. *p*-Acetamidobenzenesulphonyl chloride (Marshall *et al.*, *loc. cit.*) prepared immediately before use by interaction of acetanilide with chlorosulphonic acid and used as a wet paste (2800 g. of 46·7% ≡ 1308 g. of 100%) was added to a mixture of ice (2500 g.), and acetone (2500 c.c.) and stirred to a thin cream. *S*-Methyl*iso*thiourea sulphate (780 g.) was added and the mixture stirred for 10 minutes. Sodium hydroxide solution (456 g. in 4 l. of water) at 0° was added during 1½ hours with rapid stirring. The temperature rose to 6—7° and was maintained at this by addition of ice. The reaction mixture was stirred for 1½ hours and filtered, and the solid was washed with water and dried in a vacuum at 60—80° (yield : 1370 g.; 85%). It had m. p. 225—226°, and was sufficiently pure for the next stage. Cox (*loc. cit.*) gives m. p. 230—232°.

Conversion into p-*Acetamidobenzenesulphonylguanidine* (II, X = NHAc).—(a) *In phenol.* The above product (1350 g.) was added to a stirred melt of phenol (2400 g.) heated in an oil-bath maintained at 110°. Ammonia gas was passed into the mixture with continuous stirring for 12 hours. The suspension slowly formed a solution which later deposited a crystalline solid. The effluent gases finally gave no coloration (or only a faint yellow) with lead acetate paper. The reaction mixture was cooled to 100° and poured into a well-stirred solution of sodium hydroxide (1040 g. in 2 l. of water) mixed with ice (6000 g.). After stirring for ½ hour the solid was filtered off, washed with cold water (20 l.) until the filtrate was no longer alkaline, and dried. Yield 810 g. (67%), m. p. 248—251°. The product was used in the next stage without further purification. From *p*-nitrobenzenesulphonyl-*S*-methyl*iso*thiourea or the corresponding ethyl derivative no guanidine reaction product was obtained even though the reaction temperature was varied. *p*-Acetamidobenzenesulphonyl-*S*-ethyl*iso*thiourea under similar conditions yielded only 15—18% of the corresponding guanidine at reaction temperatures of 140—170°. At 110° unchanged *iso*thiourea only was isolated.

(b) *In absence of a solvent.* *p*-Acetamidobenzenesulphonyl-*S*-methyl*iso*thiourea (10 g.) was heated to 245—250° (oil bath temperature) and dry ammonia passed into the molten mass for 30 minutes, by which time frothing had ceased and the effluent gases gave no discoloration with wet lead acetate paper. The fused mass was heated with water (50 c.c.) until granular, cooled, made alkaline by addition of concentrated sodium hydroxide solution, and the insoluble solid filtered off. Acetylsulphanilylguanidine (4·8 g., 54%), m. p. 245—250°, was obtained. Acidification of the alkaline filtrate yielded *p*-acetamidobenzenesulphonamide (2·5 g.) identified by mixed m. p. with an authentic specimen. Amidation of *p*-acetamidobenzenesulphonyl-*S*-benzyl*iso*thiourea under similar conditions at 180—200° gave a 40% yield of acetylsulphanilylguanidine.

Hydrolysis to sulphanilylguanidine. The *p*-acetamidobenzenesulphonylguanidine obtained from the above reaction (a) was added to hydrochloric acid (3040 c.c., 1·28N) and stirred at 94—95°. After 30 minutes all the solid had dissolved; decolorising charcoal was then added, and the solution stirred at 90—94° for 10 minutes and filtered. The clear filtrate at 75° was poured into a well stirred solution of sodium hydroxide (258 g. in 2 l. of water) mixed with ice (4500 g.). After stirring for ½ hour the sulphanilylguanidine was filtered off, washed with water (*ca.* 5 l.), and dried at 60°. Yield 620 g. (91·3%), m. p. 188—189° (decomp.) (Roblin *et al.*, *loc. cit.*, give m. p. 189—190°).

Reaction C. Reaction between Sulphanilamide (*Sodium Salt*) *and* S-*Methylisothiourea Sulphate in Phenol.*—Sodium hydroxide (80 g. flake) was added with stirring to phenol (500 g.) heated at 60—80° in an oil-bath. When the reaction was complete (*ca.* 10 minutes) the mixture was heated to 150—160° and sulphanilamide (344 g.) added. Methyl*iso*thiourea sulphate (278 g.) was then added continuously during 3 hours with the temperature maintained at 160°. The hot reaction mixture was poured into water (2 l.) and heated to 45°. Concentrated hydrochloric acid (295 g.) was added, the mixture stirred until solution was complete, and xylene (200 g.) run in with vigorous agitation. The upper xylene–phenol layer was separated after standing and the lower aqueous layer treated at 45—50° with charcoal (10 g.) and filtered. The filtrate at 40° was made alkaline by addition of sodium hydroxide solution (approx. 170 g. in 400 c.c. of water). The resulting suspension was cooled to 25° and the solid filtered off. The filter cake was washed thoroughly with water, suspended in water (2·5 l.) at 90°, and cooled to 25°, and the crude sulphanilylguanidine was filtered off, washed, and dried. Yield 216 g. (50%), m. p. 182—185°. One crystallisation from water (2·5 l.) raised the m. p. to 189—190°. Sulphanilamide (35 g.) was recovered from the aqueous extract of the crude reaction mixture.

Similar reaction conditions employing *p*-acetamidobenzenesulphonamide gave a somewhat higher yield of the acetyl derivative of sulphanilylguanidine (55—60%), but from *p*-nitrobenzenesulphonamide a greatly reduced yield (2—10%) of guanidine derivative resulted. Likewise replacement of methyl*iso*thiourea sulphate by other *iso*thiourea salts caused

considerable and varying falls in yield, *viz.*, ethyl*iso*thiourea sulphate (10%), allyl*iso*thiourea hydrochloride (9—10%), β-hydroxyethyl*iso*thiourea hydrochloride (1—2%), γ-hydroxypropyl*iso*thiourea hydrochloride (2—3%), *cyclo*hexyl-*iso*thiourea hydrobromide (40—50%), benzyl*iso*thiourea hydrochloride (30%), bis-(β-*S*-*iso*thiocarbamidoethyl) ether dihydrochloride (10—12%). Cyanamide in place of the *iso*thiourea gave a 14% yield of sulphanilylguanidine, whilst nitrosoguanidine, thiourea with lead oxide, and *O*-methyl- or *O*-ethyl-urea gave yields varying from 4 to 10%. Calcium cyanamide, urea, thiourea, or ammonium thiocyanate gave products from which no sulphanilylguanidine could be isolated.

The reaction was also carried out in dichlorobenzene, and in ethylene glycol, in place of phenol, using sulphanilamide in the presence of sodium carbonate. Ammonium carbonate, sodium acetate, zinc hydroxide, or aluminium hydroxide used in place of sodium carbonate gave much reduced yields, whilst with pyridine, piperidine, quinoline, triethanolamine, or 2-aminopyridine little or no sulphanilylguanidine was obtained, although with *p*-nitrobenzenesulphonamide as reactant the last two bases gave *ca.* 10% of *p*-nitrobenzenesulphonylguanidine.

Reaction D. Reaction between Sulphanilamide and Guanidine.—Sodium hydroxide (64 g.) was dissolved in hot methyl alcohol (370 c.c.). Guanidine nitrate (196 g.) was added, and the mixture stirred for 15 minutes at 50—65°, and then cooled to 20°. The separated sodium nitrate was filtered off and washed with methyl alcohol (2 lots of 50 c.c.). The combined filtrates were stirred at 50—55° and sulphanilamide (276 g.) added. Methyl alcohol (375 c.c.) was removed by distillation from an oil-bath and *cyclo*hexanol (48 g.) then added. The oil-bath temperature was raised to 180—190° and distillation continued. Reaction commenced with evolution of ammonia when the internal temperature reached 145°. The internal temperature was then kept at 150—160° for 2 hours. The reaction mixture was poured into hydrochloric acid (1·8 l., 1·5N.), the sulphanilylguanidine precipitated by the gradual addition of sodium hydroxide solution, and the suspension cooled and filtered. The crude solid was recrystallised from water (1600 c.c.) to give sulphanilylguanidine (216 g., 63%), m. p. 188—190°.

A similar yield was obtained with guanidine carbonate in place of the guanidine solution prepared from sodium methoxide and guanidine nitrate. α-Methylguanidine and αα-dimethylguanidine (Clarke and Phillips, *J. Amer. Chem. Soc.*, 1923, **45**, 1755) in similar reactions yielded crude sulphanilylguanidine in 50% and 38% yields respectively.

Reaction between Sulphanilamide and Phenylguanidine Carbonate.—A mixture of sulphanilamide (175 g.), phenylguanidine carbonate (166 g.) (Smith, *J. Amer. Chem. Soc.*, 1927, **51**, 476) and *cyclo*hexanol (50 c.c.) was heated slowly to 160°, and maintained at 160° for 3 hours. The mixture was poured into dilute hydrochloric acid (1150 c.c. 1·75N), and filtered from insoluble matter. The filtrate was made alkaline with sodium hydroxide solution and the precipitate filtered off and digested with water (1 l.) at 90°. The undissolved solid (A) (96 g., m. p. 195—200°) was filtered off. The filtrate on cooling deposited crystalline solid (55 g., m. p. 172—177°) which after several crystallisations from water gave pure sulphanilylguanidine, m. p. 189—190°, undepressed in admixture with an authentic specimen.

(A) Repeated recrystallisation from ethanol gave β-sulphanilyl-α-phenylguanidine, m. p. 208—209° (Found: C, 53·95; H, 4·55; N, 19·2; *M*, by nitrite titre, 289. $C_{13}H_{14}O_2N_4S$ requires C, 53·6; H, 4·8; N, 19·35%; *M*, 290). No depression in m. p. was observed in admixture with a specimen prepared either by interaction of sulphanilamide and *N*-phenyl-*S*-methyl*iso*thiourea sulphate (cf. method C) or by the method of Winnek *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 1683), who, however, give the m. p. as 230—231°. It is significant that this m. p. is identical with that of the acetyl derivative of β-sulphanilyl-α-phenylguanidine prepared by any of the above methods. Also, the maximum blood concentration following oral administration of 5 mg./20 g. mouse was found to be 17·1 mg.-% for our specimens of β-sulphanilyl-α-phenylguanidine, whereas Winnek *et al.* found only 1·6 mg.-% in mice after administration of twice the above dose. (We are indebted to Dr. Spinks for the blood level determinations.)

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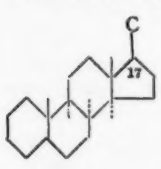
97. *The Reconversion of D-Homoandrostane Compounds into Derivatives of Androstane.*

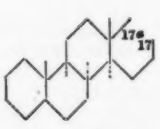
By D. A. PRINS and C. W. SHOPPEE.

Two examples of the reconversion of D-homoandrostane compounds (as II) into derivatives of androstane (as I) are recorded; in both cases ring transposition proceeds to a very limited extent, the bulk of the material remaining as D-homoandrostane compounds. Comparison of the molecular achitecture of rings C and D in (II) with that of *trans*-decahydronaphthalene fails to suggest an explanation of the practical inhibition of the rearrangement (II ⟶ I).

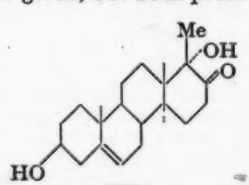
THE conversion of steroids (as I) into derivatives of D-homoandrostane or D-homoætiocholane (II), whereby the terminal 5-membered ring of the steroid nucleus becomes 6-membered, occurs readily and is frequently encountered (compare *inter alia* Ruzicka *et al.*, *Helv. Chim. Acta*, 1939, **22**, 421, 626; 1940, **23**, 364, **513**; Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 79; 1940, **62**, 489; 1941, **63**, 3127; Goldberg *et al.*, *Helv. Chim. Acta*, 1940, **23**, 376; 1941, **24**, 478, 295E; 1942, **25**, 1553; 1943, **26**, 680, 1142; Reichstein *et al.*, *ibid.*, 1941, **24**, 828, 879; Shoppee and Prins, *ibid.*, 1943, **26**, 185; 201, 2089; Shoppee, *ibid.*, 1944, **27**, 8). The reverse transformation, the regeneration of the steroid structure (I) from the D-homo-structure (II), does not appear to have been recorded; two examples are now given, but both proceed to the extent of a few per cent. only.



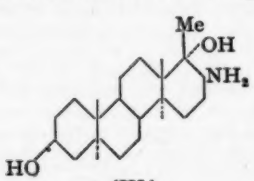
(I.)



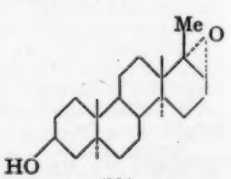
(II.)



(III.)



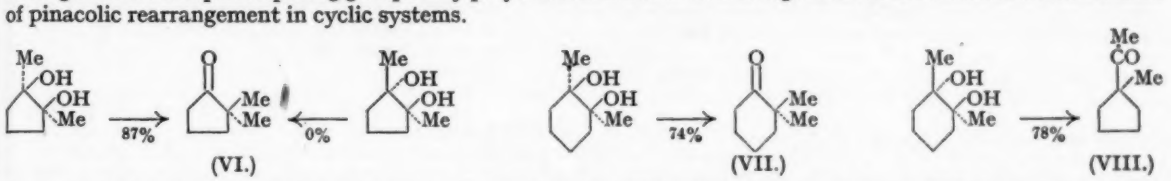
(IV.)



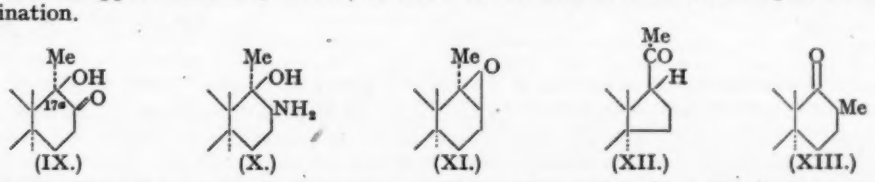
(V.)

Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1321) attempted to achieve the change (II ⟶ I) by deamination of the α-aminoalcohol (IV) obtained by complete reduction of the oxime of the hydroxyketone (III), but isolated only the oxide (V) in 63% yield, although Mousseron and Souche (*Bull. Soc. chim.*, 1935, **2**, 1102; compare *idem*, *ibid.*, 1937, **4**, 1197) had found 2-amino-1-methyl*cyclo*hexanol with nitrous acid to afford acetyl*cyclo*pentane accompanied by a little 2-methyl*cyclo*hexanone. Ruzicka and Meldahl did not, however, make a search for ketonic products possibly present in small amount.

Bartlett and Bavley (*J. Amer. Chem. Soc.*, 1938, **60**, 2416) have shown that dehydration of *cis*-1 : 2-dimethyl-*cyclo*pentane-1 : 2-diol affords 87% of the ketone (VI) but that the *trans*-diol yields only tars, and Bartlett and Pöckel (*ibid.*, 1937, **59**, 820) found dehydration of *cis*-1 : 2-dimethyl*cyclo*hexane-1 : 2-diol to give 74% of the ketone (VII) whilst the *trans*-diol furnished 78% of the isomeride (VIII). Whatever the precise interpretation of these results (compare Bartlett and Brown, *ibid.*, 1940, **62**, 2927) the general implication is that the spatial arrangement of the participating groups may play a determinative rôle in regard to the occurrence and the course of pinacolic rearrangement in cyclic systems.



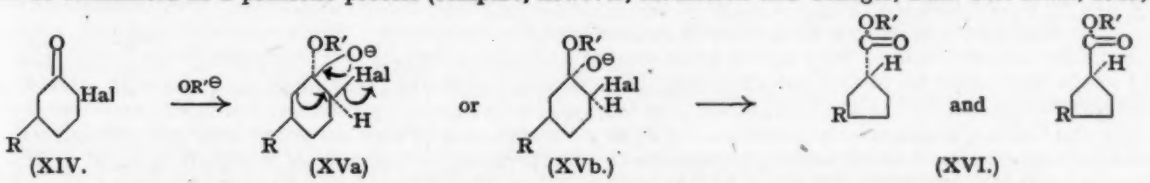
It seemed therefore of interest, when the 17*a*-epimeride (IX) of the hydroxyketone (III) became available (Stavely, *loc. cit.*; Shoppee and Prins, *loc. cit.*) to examine the behaviour of the 17*a*-epimeric α-aminoalcohol (X) on deamination.



The product resulting from the action of nitrous acid on (X) was treated with Girard's reagent-T. Non-ketonic material formed the bulk of the product and furnished the beautifully crystalline *oxide* (XI), characterised as the *acetate*, but no trace of the corresponding diol (Stavely, *loc. cit.*; compare also Godschot and Mousseron, *Bull. Soc. chim.*, 1934, **1**, 1925) was found. The acetoxy-oxide could not be cleaved by hot acetic acid (compare Ruzicka and Meldahl, *loc. cit.*, who were able to split the 17 : 17*a*-epimeric oxide (V) under these conditions) and was recovered unchanged; use of acetic acid containing 5% hydrochloric acid was also ineffective but hydrolysed the 3(β)-acetoxy group to regenerate the oxide (XI). The betaine-hydrazones were fractionally hydrolysed at pH 3 and pH ≪ 1 to give ketonic fractions (K_1 and K_2). Fraction K_1 (21 mg.) was non-crystalline, but on chromatographic analysis gave traces of the oxide (XI), a very small quantity of an unidentified ketone, and a little *allo*pregnane-3(β)-ol-20-one (XII). Fraction K_2 (25 mg.) was crystalline and after chromatographic purification afforded a ketone which, by exclusion, would appear to be 17-*methyl-D-homo-androstane*-3(β)-*ol*-17a-*one* (XIII).

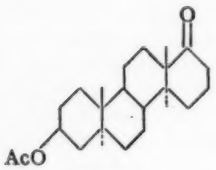
The results of Bartlett *et al.* suggest that of the four C_{17}-isomerides represented by (IV) and (X), only 17(β)-amino-(IV) and 17(α)-amino-(X) should give (XII) whilst only the two remaining epimerides should furnish (XIII); it would seem that the oxides (V) and (XI) could result respectively from either of the 17-amino epimerides represented by (IV) and (X). The configuration of the amino group in (IV) and (X) is not known, and, although both the bases and their oxime precursors were prepared under the same conditions, it is uncertain whether they were homogeneous or mixtures of C_{17}-epimerides. Owing to this configurational uncertainty and its possible significance, we have attempted to eliminate, or at least to minimise, the influence upon rearrangement of the type (II ⟶ I) of the geometrical arrangement of the groups concerned as follows.

The general reaction, originally described by Favorski (*J. Russ. Phys. Chem. Soc.*, 1912, **43**, 580), whereby α-halogenoketones by treatment with alkalis undergo ring-contraction to give carboxylic acids or their esters, can be formulated as a pinacolic process (compare, however, Mousseron and Granger, *Bull. Soc. chim.*, 1943,

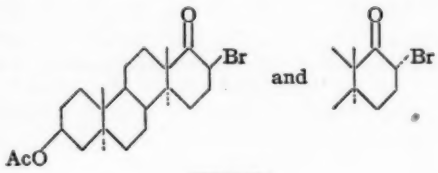


10, 42; also Aston and Greenberg, *J. Amer. Chem. Soc.*, 1940, **62**, 2590); and appears to provide a comparable chance that the two configurations (XVa, XVb; R = H) can arise by addition of the nucleophilic anion. Mousseron, Granger, and Bourrel (*Bull. Soc. chim.*, 1939, **6**, 607) starting from the chloroketone (XIV; R = Me) have isolated both the acids corresponding to (XVI), whilst the production of a similar pair of *trans*-hydrindane-2-carboxylic acids from 3-chloro-*trans*-β-decalone has been reported by Cauquil and Tsatsas (*ibid.*, 1945, **10**, 47).

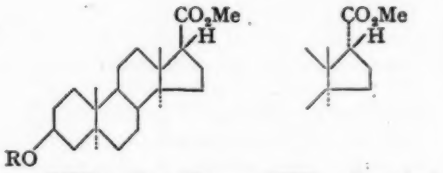
To realise the change (II ⟶ I) by application of the Favorski reaction, we utilised the stereoisomeric bromo-acetoxyketones corresponding to (XVIII) derived from D-homoandrostane-3(β)-ol-17a-one acetate (XVII) (Goldberg and Monnier, *Helv. Chim. Acta*, 1940, **23**, 376; see also Goldberg and Wydler, *ibid.*, 1943, **26**, 1142). The isomerides represented by (XVIII) were difficult to separate, and the mixture of crystalline bromo-acetoxy-ketones was used for treatment with various alkaline reagents.



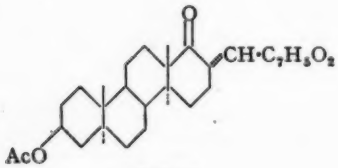
(XVII.)



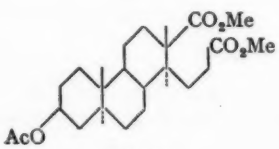
(XVIII.)



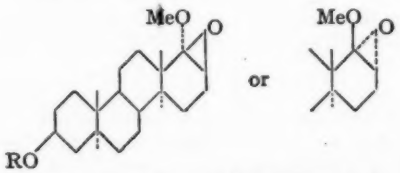
(XIXa; R = H.) (XIXb; R = Ac.) (XIXc; R = Ac.)



(XXI.)



(XXII.)



(XXa; R = H.) (XXb; R = Ac.)

The action of sodium methoxide in methanol on (XVIII) dissolved in ether at 20° yielded no acid fraction directly; the neutral product gave a substance $C_{21}H_{34}O_3$, which is probably one of the stereoisomeric oxides (XXa). The neutral mother liquors could not be hydrolysed by potassium hydroxide to furnish any acidic substance so that the neutral fraction could not have contained the ester (XIXa). The unavoidable presence of small amounts of methanol may be concerned with the non-production here of the ester (XIXa) (compare Aston and Greenberg, *loc. cit.*).

Employment of potassium bicarbonate in methanol (Marker and Wagner, *J. Amer. Chem. Soc.*, 1942, **64**, 216) also yielded no acidic fraction; the neutral fraction gave a compound, $C_{23}H_{36}O_4$, which however cannot be the unknown ester (XIXc) because it could not be hydrolysed to an acid; the substance did not appear to react with semicarbazide and is probably one of the pair of oxides represented by (XXb). A substance, $C_{24}H_{36-38}O_5$, m. p. 220—222°, was also isolated chromatographically; this involves an increase of 2 C and 2 O atoms with respect to (XVII) ($C_{22}H_{34}O_3$) and suggests that additon of methanol to (XXb) may have occurred (compare Aston and Greenberg, *loc. cit.*).

Treatment with methanolic potassium hydroxide, which should lead directly to acids, gave a small acidic fraction; after esterification with diazomethane, chromatographic analysis furnished traces of an unidentified methyl ester, m. p. 225°, which was eluted only with acetone. Other fractions of the chromatogram failed to crystallise by inoculation with methyl 3(β)-hydroxyætio*allo*cholanate (XIXa). The neutral fraction was discarded.

Use of dry powdery sodium methoxide in anhydrous dioxan and alkaline hydrolysis of the neutral product furnished a mixture of solid acids; chromatographic analysis of the acetylated methyl esters yielded a very small amount of methyl 3(β)-acetoxyætio*allo*cholanate (XIXb), a little *methyl* 3(β)-*acetoxy*allo*homobilianate* (XXII), and traces of an unidentified methyl ester, m. p. 110—112°. The neutral hydrolysis product was not examined.

For comparison with the ester (XXII), a genuine specimen was synthesised as follows: the acetoxyketone (XVII) was converted into the piperonylidene derivative (XXI) and, after reacetylation, this was treated with ozone in acetic acid and the ozonide oxidised in acetic acid with chromium trioxide; esterification with diazo-methane, acetylation, and chromatographic purification of the product furnished the dimethyl ester (XXII), double m. p. 139° and 156°.

The rearrangement (II ⟶ I) can thus be realised but proceeds with very considerable difficulty and to a very limited extent, the bulk of the material remaining as D-homoderivatives. It was pointed out by Wightman (*J.*, 1925, 1421) that the *trans*-decahydronaphthalene skeleton could exist in 3 forms, chair-chair (B), chair-boat (E), and boat-boat (G); in the strict strain-free sense all forms containing the chair are rigid, *i.e.*, B and E are rigid and G has a little strain-free motion; on Mohr's postulate, all 3 forms are interconvertible through a very small energy barrier, B and E tending to pass into G. These characteristics are not obviously changed when the *trans*-decahydronaphthalene structure is extended to afford the D-homoandrostane structure (as II). The ready transformation of the *trans*-decahydronaphthalene skeleton to that of *trans*-hydrindane reported by Cauquil and Tsatsas (*loc. cit.*) may not be precisely analogous to the rearrangement (II ⟶ I), but the cause of the difficulty in the latter case remains obscure. It is, however, known (compare Reichstein and Gatzi, *Helv. Chim. Acta*, 1940, **23**, 1480; Shoppee, *ibid.*, 1941, **24**, 351) that mutually remote parts of the steroid system (I) can influence one another, and similar effects may well be operative in the D-homoandrostane system (II).

Experimental.

(All m. ps. were determined thermoelectrically on a Kofler block and are corrected: Limits of error ±2°. All solvents used for chromatographic separations were rigorously purified and dried.)

17*a*-Methyl-Δ^5-D-homoandrostene-3(β) : 17*a*(β)-diol-17-one (IX) was prepared from 17-ethynyl-Δ^5-androstene-3(β) : 17(α)-diol by the method of Stavely (*J. Amer. Chem. Soc.*, 1941, **63**, 3127) as long prisms, m. p. 188—190°, from acetone–ether; a genuine specimen previously prepared by Shoppee and Prins (*Helv. Chim. Acta*, 1943, **26**, 201) and labelled m. p. 176—178° was found now to have m. p. 188—190°, and a mixture of the two preparations had m. p. 188—190°. The *oxime* was obtained by refluxing the dihydroxy-ketone (620 mg.) for 3 hours with the filtrate obtained by dissolving hydroxylamine hydrochloride (620 mg.) and crystalline sodium acetate (1·24 g.) in methanol (25 c.c.). The solution was cooled, poured into water, and the product filtered off and dried in a vacuum. Recrystallisation from alcohol gave successive crops of colourless prisms m. p. (i) 283°, (ii) 285°, (iii) 285°, (iv) 280—283° all decomp. (yield, 555 mg.) (Found (after drying at 80°/0·01 mm.): C, 72·99; H, 9·82; N, 4·12. $C_{21}H_{33}O_3N$ requires C, 72·60; H, 9·60; N, 4·03%).

17-*Amino*-17a-*methyl*-*D*-*homoandrostane*-3(β) : 17a(β)-*diol* (X).—$PtO_2.H_2O$ (100 mg.) suspended in acetic acid (12 c.c.) was prehydrogenated; the foregoing oxime (550 mg.) suspended in absolute alcohol (8 c.c.) was added, and the whole shaken in hydrogen at 20°. The reaction was stopped after absorption of 107 c.c. of hydrogen (= $3H_2$) in 1½ hours, and the solution filtered and largely evaporated under reduced pressure at 40°. Water was added, a small precipitate filtered off and rejected, and the clear filtrate made slightly alkaline with 2N-NaOH. The *base* so precipitated was filtered off and dried in high vacuum: it was very insoluble in chloroform, acetone, and dioxan, but separated from alcohol by concentration in microprisms, m. p. 240—244° [Found (after drying at 80°/0·01 mm.): C, 74·80; H, 10·89. $C_{21}H_{37}O_2N$ requires C, 75·18; H, 11·11%].

Deamination. The amine (400 mg.) was treated with sodium nitrite in 2N-AcOH as described by Ruzicka and Meldahl (*Helv. Chem. Acta*, 1941, **24**, 1321) but with mechanical stirring. The reaction product was extracted with ether, the extract washed with 2N-Na_2CO_3, and with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in methanol (8 c.c.) and, after addition of acetic acid (0·60 c.c.) and Girard's reagent-T (600 mg.), refluxed for 20 minutes. The well-cooled solution was poured into a mixture of 2N-NaOH (4·90 c.c.) and ice-water (*ca.* 100 c.c.) and immediately extracted with ether. The extract was washed with water, 2N-Na_2CO_3, and again with water, dried (Na_2SO_4), and evaporated to yield non-ketonic material (201 mg.). The aqueous solution was made just acid to Congo red with hydrochloric acid, allowed to stand for ½ hour, partly evaporated under reduced pressure to remove methanol, and extracted with ether. The extract was washed with water, 2N-Na_2CO_3, and again with water, dried (Na_2SO_4) and evaporated to furnish fraction K_1 (21 mg.). Finally the aqueous solution was mixed with 10% of its volume of concentrated hydrochloric acid and allowed to stand for ½ hour. The solution was then extracted with ether, the extract washed as above, dried, and evaporated to afford fraction K_2 (25 mg.) which crystallised largely on keeping, m. p. *ca.* 150°.

The non-ketonic fraction crystallised by keeping and, recrystallised from alcohol, gave shining pyramids of 17(β) : 17a(β)-*epoxy*-17a-*methyl*-*D*-*homoandrostane*-3(β)-*ol* (XI), m. p. 210°, which failed to analyse satisfactorily (cf. the experience of Ruzicka and Meldahl with the 17(α) : 17*a*(α)-isomeride). (Found (after sublimation at 160—170°/0·001 mm.): C, 80·35; H, 10·60. $C_{21}H_{34}O_2$ requires C, 79·20; H, 10·76%). The *acetate*, prepared by treatment with acetic anhydride in pyridine for 18 hours at 20°, was crystallised twice from methanol and formed clusters of colourless prisms, m. p. 171°, $[\alpha]_D^{16°}$ −31·9 ± 3° (*c* = 0·785 in acetone) (Found (after sublimation at 150—160°/0·001 mm.): C, 76·60; H, 9·90. $C_{23}H_{36}O_3$ requires C, 76·62; H, 10·06%). The epoxyacetate was recovered unchanged, m. p. 170°, after refluxing for 2 hours with CrO_3-stable acetic acid (cf. Ruzicka and Meldahl, *loc. cit.*) (Found: C, 76·10; H, 10·02%); use of "AnalaR" acetic acid containing 5% of concentrated hydrochloric acid was also ineffective, but here hydrolysis of the 3-acetoxy group occurred to regenerate the oxide, m. p. 210°. The ketonic fraction K_1 was non-crystalline; it was dissolved in benzene (0·5 c.c.) and introduced on to a column of alumina (Spence (activity I–II, according to the scale suggested by Brockmann and Schodder, *Ber.*, 1941, **74**, 73), 650 mg.) prepared in pentane (5 c.c.). The chromatogram was developed using the "Durchlauf" method as set out in Table I.

Table I.

Fraction.	Eluant (2·5 c.c.).	Eluate.
1, 2	Benzene–pentane (1 : 10)	—
3	,, (1 : 1)	—
4, 5	Benzene	—
6	Ether–benzene (1 : 15)	Crystallised spontaneously — Recryst. ether–pentane in prisms, m. p.
7	,, ,,	,, by inoculation with Fr. 6 — 157—161°.
8	,, ,,	—
9, 10	,, (1 : 7)	Crystallised spontaneously : recryst. ether–pentane, m. p. 200—207°.
11, 12	,, (1 : 3·5)	,, ,, ,, ether–pentane, m. p. 195—203°.
13, 14	,, (1 : 1)	,, by inoculation : recryst. ether–pentane, m. p. 170—200°.
15, 16	Ether	,, ,, ,, ether–pentane, m. p. 170—195°.
17	Acetone–ether (1 : 4)	Little oil.
18	,, (1 : 1)	,,
19	Acetone	Trace of oil.
20	,,	—

The substance (2 mg.) present in fractions 6 and 7 could not be identified; the m. p. was depressed to 135° on admixture with the ketone (XIII) of m. p. 163°. Fractions 9—12 furnished the oxide (XI) (3 mg.), no m. p. depression being observed on admixture with this compound, and the various melts crystallising immediately on slight cooling. Fractions 13—16 appeared to be mixtures of the oxide (XI) with some other substance(s); fractions 13—18 and the mother-liquors from fractions 11 and 12 were therefore united (9 mg.) and re-chromatographed on a column of alumina (Merck-Brockmann (activity III—IV), 450 mg.) prepared in benzene. Elution with ether–benzene mixtures (1 : 4, 1 : 2) furnished small quantities of the oxide (XI), m. p. 205—210°, whilst ether afforded *allo*pregnane-3(β)-ol-20-one (XII) (2 mg.) as leaflets (from ether–pentane), m. p. 193—195°, which did not depress the m. p. of a genuine specimen. Elution with acetone–ether mixtures and with acetone gave only traces of oil which could not be induced to crystallise.

The ketonic fraction K_2 was crystalline, m. p. *ca.* 150°; it was dissolved in benzene (0·5 c.c.) and purified chromatographically on a column of alumina (Spence (activity I–II), 750 mg.) prepared in pentane (5 c.c.), using 2·5 c.c. of each eluant. Elution with ether–benzene (1 : 2) gave traces of crystalline material, and with ether–benzene (1 : 1) furnished 3 fractions (6, 7, and 8) which crystallised spontaneously on evaporation, whilst ether afforded further traces of crystalline material. Fractions 6, 7, and 8 were recrystallised from ether–pentane to give in each case felted needles m. p. 160—163°; they were united and crystallised from ether–pentane to furnish 4 mg. of a ketone, m. p. 163—165°, presumed by exclusion to be 17-*methyl*-D-*homoandrostane*-3(β)-*ol*-17a-*one* (XIII). For analysis the substance was sublimed at 150°/

0·001 mm. (Found: C, 79·45; H, 10·74. $C_{21}H_{34}O_2$ requires C, 79·20; H, 10·90%). Subsequent eluates obtained by elution with acetone–ether mixtures and with acetone gave no appreciable residues. The second crop of the ketone (XIII) (2 mg.) had m. p. 160—163° and was converted into the semicarbazone, m. p. 270—273°.

D-Homoandrostane-3(*β*)-ol-17*a*-one acetate (XVII) was originally obtained from Δ^5-androstene-3(*β*)-ol-17-one acetate (dehydro*iso*androsterone acetate) by the method of Goldberg and Monnier (*loc. cit.*; cf. Goldberg and Wydler, *loc. cit.*) with slight modification. The cyanohydrin, m. p. 185—186° (decomp.), by complete hydrogenation gave the acetate of the acetoxyamine (X), which separated from methanol–ether in prisms becoming opaque at 150—160°, undergoing transformation at 220—225° without melting to iridescent plates, m. p. 236—237° (without decomp. (cf. Goldberg and Monnier)), the melt recrystallising immediately on slight cooling. Subsequent fractions exhibited the same behaviour, but the final m. p. rose to 242—244° and 244—246°. Deamination gave the acetoxy-ketone (XVII); after crystallisation from ether–pentane and drying at 85°/0·02 mm., it had m. p. 118—120°, $(\alpha)_D^{14}$ $-50° \pm 2°$ (c = 1,050 in methanol). Chromatographic purification eliminated traces of the isomeric D-homoandrostane-3(*β*)-ol-17-one acetate, but failed to give the m. p. 124—125° and $[\alpha]_D^{20°}$ −45° found by Goldberg and Monnier. Since catalytic reduction in acetic acid leads to quite considerable amounts of ætiocholane compounds (Reichstein and Lardon, *Helv. Chim. Acta*, 1941, **24**, 955; Wenner and Reichstein, *ibid.*, 1944, **27**, 24), the acetoxyketone (XVII) was obtained from androstane-3(*β*)-ol-17-one acetate (*iso*androsterone acetate).

Androstane-3(*β*)-ol-17-one acetate, double m. p. 97° and 102—104°, (3 g.) was dissolved in 96% alcohol (50 c.c.), and the solution was cooled to 20°, and finely powdered potassium cyanide (5·9 g. = 10 mols.) added. Acetic acid (5·4 c.c. = 9·5 mols.) was then added gradually with mechanical stirring, and finally 0·1 c.c. of triethylamine (cf. Lapworth, *J.*, 1928, 2533). After 16 hours at 15°, the mixture was poured into water (500 c.c.) containing acetic acid (2 c.c.) with stirring, and the precipitate filtered off, washed with water, and dried in a vacuum. Crystallisation from ether gave the *cyanohydrin* (1·80 g.) as long prisms, m. p. 125—126° (decomp.), $[\alpha]_D^{14°}$ $-28° \pm 1·5°$ (c = 1·624 in alcohol) (Found (after drying at 60°/0·01 mm.): C, 73·10; H, 9·06. $C_{22}H_{33}O_2N$ requires C, 73·49; H, 9·25%). The mother liquor yielded further small crops of crystals (380 mg. and 290 mg.) probably consisting essentially of the epimeric *cyanohydrin*, m. p. 146—148° (decomp.), $[\alpha]_D^{14°}$ $-24·7° \pm 1·5°$ (c = 1·416 in alcohol) (Found (after drying at 60°/0·01 mm.): N, 3·90. $C_{22}H_{33}O_2N$ requires N, 3·90%). The cyanohydrin (1·79) dissolved in pure acetic acid (25 c.c.) was shaken with Pt (from 350 mg. of $PtO_2.H_2O$) in hydrogen at 20° (H_2 absorbed, 221 c.c. Calc.: 233 c.c.). After filtration, the solution was evaporated at 35—40°/10 mm., and the residual syrup dissolved in methanol (7·5 c.c.); concentration to about $\frac{1}{4}$ volume and addition of ether gave the acetoxyamine acetate (1·81 g.) as prisms becoming opaque at 160° and transformed at 225° to flat iridescent plates, m. p. 243—246° with immediate recrystallisation of the melt. This procedure is much to be preferred to that given by Goldberg and Monnier, which involves evaporation under reduced pressure of an aqueous solution of the acetoxyamine acetate whereby extensive frothing occurs only partially overcome by addition of *n*-octyl alcohol. Deamination of the acetoxyamine acetate furnished 1·39 g. of crude product, which by crystallisation from ether–pentane gave D-homoandrostane-3(*β*)-ol-17*a*-one acetate (770 mg.), m. p. 123—125°, $[\alpha]_D^{15°}$ $-45·3° \pm 1°$ (c = 2·192 in methanol) (material sublimed at 130—140°/0·02 mm.). A further quantity of the same degree of purity was obtained from the mother liquor by chromatography, together with a little D-homoandrostane-3(*β*)-ol-17-one, m. p. 104°; mixtures of these two acetoxyketones do not give m. p. depressions.

17-*Bromo-D-homoandrostane*-3(*β*)-*ol*-17*a*-*one acetate* (XVIII). The acetoxyketone (680 mg.) dissolved in acetic acid (2 c.c.) was treated with a solution of bromine (314 mg. ≒ 1 mol.) in acetic acid (1·0 c.c.) dropwise. The *bromo-acetoxyketone* crystallised spontaneously; after addition of ether, it was filtered off and washed with ether–pentane (1 : 1) (530 mg., m. p. *ca.* 240°); recrystallisation from chloroform–ether or dioxan–ether gave shining plates (365 mg.), m. p. 246—248°, $[\alpha]_D^{14°}$ $-31·7° \pm 2°$ (c = 1·483 in chloroform) (Found (after drying at 80°/0·01 mm.): Br, 18·85. $C_{23}H_{33}O_3Br$ requires Br, 18·79%). The mother liquor by concentration gave only a small quantity of crystals; the combined mother liquors by complete evaporation furnished 520 mg. of material which was dissolved in benzene (2 c.c.) and chromatographed on a column of neutralised * alumina (16 g.) prepared in pentane. Elution with benzene–pentane (1 : 1), benzene, and ether–benzene mixtures containing 1—5% of ether yielded crystalline fractions which failed to melt sharply; thus fraction 9 (obtained with benzene), after recrystallisation from ether, had m. p. 182—185° but traces of material in the melt survived to *ca.* 200°; these crystals had $[\alpha]_D^{14°}$ $-55·5° \pm 3°$ (c = 1·188 in chloroform) and appeared to consist largely of the 17-*epimeric bromo-acetoxyketone* (Found: C, 62·62; H, 8·01. $C_{23}H_{33}O_3Br$ requires C, 62·11; H, 7·82%). As separation appeared difficult, the various crystalline fractions were combined and reduced with zinc in acetic acid in the presence of sodium acetate to afford the acetoxyketone, m. p. 123—124°.

Action of Alkaline Reagents on the Bromo-acetoxyketones (XVIII).—(*a*) The compound (XVIII), m. p. 246—248° (170 mg.), in dry ether was added to a cold solution of sodium methoxide (from 230 mg. " molecular " sodium and dry methanol (1 c.c.)). Sodium bromide was immediately precipitated, and, after standing at 15° for 2 hours, the reaction mixture was poured into ice–water (10 c.c.) containing 2N-HCl (5·5 c.c.), extracted with ether, and separated into neutral and acidic fractions. The neutral fraction (130 mg.) crystallised on concentration of the ether solution; the crystals were filtered off and recrystallised from acetone in prisms, m. p. 226° after softening from 218°, $[\alpha]_D^{15°}$ $-38·2° \pm 4°$ (c = 0·524 in acetone) (Found (after sublimation at 180°/0·01 mm.): C, 74·70; H, 9·70. $C_{21}H_{34}O_3$ requires C, 75·39; H, 10·25%). The compound did not appear to react with semicarbazide acetate and is regarded as 17 : 17a-*epoxy*-17a-*methoxy-D-homoandrostane*-3(*β*)-*ol* (XXa). The united mother liquors were evaporated and the residue refluxed with 3·3% methanolic potassium hydroxide (2 c.c.) for 2 hours; after addition of a few drops of water and saturation with carbon dioxide, methanol was removed under reduced pressure, and the product acidified, extracted with ether, and separated into in neutral and acidic fractions. No acidic fraction was obtained; the neutral fraction was rejected.

(*b*) The compound (XVIII) (m. p. *ca.* 240°; 350 mg.) was dissolved in methanol (20 c.c.), a solution of potassium bicarbonate (1 g.) in water (4 c.c.) added, and the mixture refluxed on the steam-bath for 3 hours. After removal of methanol under reduced pressure and addition of water, the product was extracted with ether, and the extract washed with water, dried (Na_2SO_4), and evaporated. The residual oil, dissolved in a little ether–pentane, was left overnight at −15°; the crystals which separated were washed with cooled ether–pentane to give 17 : 17a-*epoxy*-17a-*methoxy-D-homoandrostane*-3(*β*)-*ol acetate* (XXb) as needles, m. p. 164—166°. For analysis the compound was again recrystallised from methanol; it then had m. p. 164—166°, and sublimed at 140°/0·02 mm. (Found: C, 73, 17; H, 9·53. $C_{23}H_{36}O_4$ requires C, 73·37; H, 9·63%). The compound could not be hydrolysed by methanolic potassium hydroxide to yield an acid, and did not appear to react with semicarbazide acetate. Chromatography of the residue from the original ether–pentane mother liquor afforded with benzene–pentane (1 : 2) a small amount of the foregoing oxide, and with benzene a small quantity of a *substance*, which, recrystallised several times from ether–pentane, formed flat prisms transformed at *ca.* 205° to hair-like needles, m. p. 210—212° with partial recrystallisation and final melting at 220—222° (Found (after drying at 100°/0·02 mm.): C, 71·09; H, 8·92. $C_{24}H_{36}O_5$ requires C, 71·25; H, 8·9; $C_{24}H_{38}O_5$ requires C, 70·90; H, 9·42%). The potassium bicarbonate aqueous liquor on acidification and extraction furnished no acidic material.

* Al_2O_3 (Merck–Brockmann) was digested with 2N-HNO_3, filtered off, washed well with water, and twice refluxed with MeOH; the oxide was filtered off, freed from MeOH in a vacuum and reactivated at 250°/10 mm.

(*c*) The compound (XVIII) (m. p. *ca.* 240°; 160 mg.) was refluxed with 3·3% methanolic potassium hydroxide (containing 3—4% water) (5 c.c.) for 1 hour; after adding a few drops of water, methanol was removed under reduced pressure. Part of the product was insoluble in hot chloroform, but soluble in warm water; the reaction mixture was therefore extracted with chloroform–ether and the extract washed with water. The washing was mixed with the alkaline aqueous liquor and acidified; a precipitate then formed. The acid(s) were extracted with chloroform–ether, and the extract dried and evaporated to afford 40 mg. of oil which was esterified with diazomethane in ether. Chromatography of the product (eluants: benzene–pentane (1 : 1), benzene, ether–benzene mixtures (2—40% ether), ether, and acetone–ether (1 : 1)) furnished only oily fractions which failed to crystallise when inoculated with methyl 3(*β*)-hydroxyætio*allo*cholanate; elution with acetone and chloroform–acetone (1 : 1) gave traces of an unindentified methyl ester, m. p. *ca.* 225°. The neutral product of the reaction was not further examined.

(*d*) The compound (XVIII) (m. p. 235°; 665 mg.) was dissolved in warm dioxan (10 c.c. freshly distilled over Na) and dry powdery sodium methoxide (cf. Komppa, *Annalen*, 1909, **368**, 137) (*ca.* 200 mg.) was introduced. After standing for 48 hours at 15° with rigid exclusion of moisture, dioxan was removed under reduced pressure. The yellow residue was treated with ice–water, and on addition of 2N-HCl became nearly colourless. Extraction with chloroform, and washing of the extract with 2N-Na_2CO_3 gave an acidic gum (20 mg.) which was rejected. Evaporation of the chloroform extract furnished a yellow oil (570 mg.) which was refluxed for 1 hour with 3·3% methanolic potassium hydroxide (10 c.c.). After addition of a little water, methanol was removed under reduced pressure to leave a yellow product partially insoluble in ether–chloroform; the resulting yellow powder was insoluble in cold water, and was filtered off and washed with chloroform. The ether–chloroform solution, containing unsaponifiable material, was not further examined. The potassium salts were dissolved in hot water and acidified with 2N-HCl (Congo red) to furnish a nearly colourless precipitate of solid acids (44 mg.), m. p. 160—170° (unsharp).

The dried mixture of acids was dissolved in dioxan, esterified with diazomethane in ether, and the residue obtained by evaporation refluxed with acetic anhydride for ½ hour. Acetic anhydride was evaporated in a vacuum, the last traces were removed in a high vacuum, and the product, dissolved in benzene (0·5 c.c.), was chromatographed by the " Durchlauf " method on a column of alumina (Merck–Brockmann (activity III–IV), 1·5 g.) prepared in pentane.

TABLE II.

Fraction.	Eluant (5 c.c.).	Eluate.
1	Benzene–pentane (1 : 20)	—
2	,, (1 : 10)	Trace of oil.
3	,, (1 : 4)	Crystallised spontaneously; recryst. methanol, m. p. 110—111°.
4, 5	,, ,,	Little oil, failed to crystallise.
6, 7	,, (1 : 2)	Oil, crystallised from methanol; plates, m. p. 146—148°.
8, 9	,, (1 : 1)	,, ,, ,, double m. p. 139° and 156°.
10, 11	Benzene	Oil, failed to crystallise.
12	Ether–benzene (1 : 1)	,, ,, ,,
13	Ether	,, ,, ,,

Fractions 6 and 7 gave methyl 3(*β*)-acetoxyætio*allo*cholanate (1·5 mg.) (XIXb), which gave no depression with a genuine specimen, m. p. 148—150°; the quantity was insufficient to determine the specific rotation, but the opportunity was taken to measure this constant, which has not previously been recorded, for the genuine specimen: $[\alpha]_D^{18°}$ + 42° ± 2° (*c* = 1·064 in acetone).

Fractions 8 and 9 furnished an ester (4 mg.) exhibiting a double m. p. and shown to be *methyl* 3(*β*)-*acetoxy*allo*homobilianate* (XXII) by mixed m. p. with a genuine specimen, and by the specific rotation $[\alpha]_D^{15°}$ −6° ± 6° (*c* = 0·308 in acetone) (Found (after distillation at 160—170°/0·02 mm.): C, 68·10; H, 9·20. $C_{24}H_{38}O_6$ requires C, 68·22; H, 9·06%).

The trace of ester, m. p. 110—111°, from fraction 3 (<1 mg.) was insufficient for further examination.

Methyl 3(*β*) *Acetoxy*allo*homobilianate* (XXII) *from D-Homoandrostane-*3(*β*)*-ol-*17*-one Acetate* (XVII).—The acetoxy-ketone (XVII) (125 mg.) and piperonal (75 mg.) were dissolved in methanol (2·5 c.c.), 10N-KOH (0·1 c.c.) added, and the mixture left at 15° for 16 hours. The yellow needles which separated were filtered off (40 mg.), m. p. 190—192°; the mother-liquor despite its yellow colour gave an oily residue (97 mg.) which consisted mainly of unchanged acetoxy-ketone since chromatographic purification furnished this compound (80 mg.), m. p. 124°, mixed m. p. 124°. The piperonylidene derivative was refluxed with acetic anhydride for ½ hour, and the residue obtained by complete evaporation (m. p. 190° was dissolved in chloroform and treated with ozonised oxygen for ½ hour at 0°. After removal of chloroform under reduced pressure, the product was taken up in acetic acid (0·5 c.c.) and a solution of chromium trioxide in acetic acid (1 c.c. of 2%) added; the mixture, after standing overnight at 15°, was worked up in the usual manner to give an oil (17 mg.), which was esterified with diazomethane in ether. The product obtained by evaporation was dissolved in benzene (0·5 c.c.) and introduced onto a column of alumina (Merck–Brockmann, 0·5 g.) prepared in pentane. Elution with benzene–pentane (1 : 2 and 1 : 1) gave eluates which crystallised by rubbing with a trace of methanol; these fractions were united and crystallised twice from methanol to give plates (3 mg.) of the methyl ester (XXII), m. p. 139—140° with resolidification to prisms, m. p. 156°, recrystallising at 154° and remelting at 155—156°, $[\alpha]_D^{20°}$ −8° ± 4° (*c* = 0·250 in acetone on material dried at 80°/0·02 mm.). The ester was recovered from the acetone solution and distilled at 170°/0·02 mm. for analysis (Found: C, 68·08; H, 9·14%).

We wish to thank Dr. K. Miescher of CIBA Limited, Basle, for gifts of dehydro*iso*androsterone and *iso*androsterone acetates, Professor Dr. L. Ruzicka, For. Mem. R.S., for microanalytical facilities at the Eidg. Techn. Hochschule, Zürich, and Prof. Dr. T. Reichstein for the hospitality of his Institute; one of us (C. W. S.) also desires to acknowledge the award of a Rockefeller Research Fellowship, during the tenure of which part of this work was carried out, and the generous support of the British Empire Cancer Campaign and the Jane Coffin Childs Memorial Fund.

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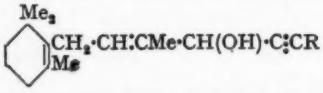
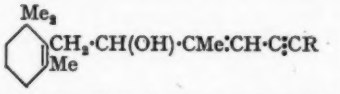
98. *Studies in the Polyene Series. Part XXIII. Condensation of the C_{14}-Aldehyde [3-(2′ : 6′ : 6′-Trimethylcyclohexenyl)-1-methylcrotonaldehyde] with 1-Hexyne and 2-Methoxyhex-3-en-5-yne.*

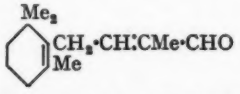
By J. Cymerman, Sir Ian Heilbron, E. R. H. Jones, and R. N. Lacey.

Condensations between the C_{14}-aldehyde (III) and both 1-hexyne ($C_4H_9\cdot C{:}CH$) and 2-methoxyhex-3-en-5-yne [$CH{:}C\cdot CH{:}CH\cdot CH(OMe)Me$] can be effected in good yields. The resulting carbinols [I; R = C_4H_9 and $CH{:}CH\cdot CH(OMe)Me$ respectively] are rearranged (to II) in the expected manner with acids, but on elimination of

(I.)   (II.)

water from (II), by treating the corresponding chloro-compounds with diethylaniline, the anticipated fully conjugated polyenynes are not formed. Since *iso*geronic acid is produced in each case on ozonolysis of the final products, it must be concluded that the failure to obtain conjugated systems of the vitamin A type is due to migration of the ring double bond into the α-position (*i.e.*, corresponding to that in α-ionone) at some undetermined stage in the syntheses.

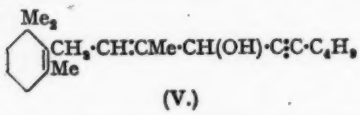
In Part V of this series (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727) a scheme for the synthesis of polyene compounds related to vitamin A was propounded, one variant of which involved the condensation of the C_{14} aldehyde (III), derived from β-ionone, with conjugated acetylenylvinylcarbinols such as (IV). Experiments along these lines have now been carried out, and this paper contains an account of condensations with the readily available 1-hexyne and 2-methoxyhex-3-en-5-yne (Heilbron, Jones, and Weedon, *J.*, 1945, 82).

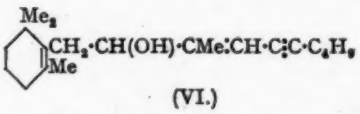
(III.)  $HC{:}C\cdot CMe{:}CH\cdot CH_2\cdot OH$ (IV.)

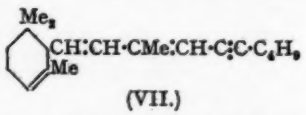
It was early appreciated that, as in all similar investigations in this series, reliable and significant results could only be expected by employing aldehyde of indubitable purity, regenerated from a pure crystalline derivative, as the starting material. Hydrolysis of the previously described thiosemicarbazone, even with 35% sulphuric acid and light petroleum (b. p. 100—120°), was effected only with difficulty and in very poor yield. Although we had hitherto failed to prepare a semicarbazone of the aldehyde, this proved possible with the material regenerated from the thiosemicarbazone. Subsequently, carefully fractionated aldehyde also yielded the *semicarbazone*, m. p. 148—150°, when the preparation was seeded. The light absorption properties of this derivative were in accord with those usually exhibited by the semicarbazones of αβ-unsaturated aldehydes (cf. Evans and Gillam, *J.*, 1943, 565). Refluxing the semicarbazone with 15% sulphuric acid and light petroleum (b. p. 80—100°) sufficed to regenerate the pure aldehyde in 90% yield.

[It may be noted here that the crystalline acid (obtained from pure β-ionone) gave only a poor yield of a very inhomogeneous aldehyde, possibly due to the difficulty of ensuring sufficient contact between the acid and the copper bronze during decarboxylation.]

Condensation of the pure aldehyde (III) and 1-hexyne gave a 90% yield of the *carbinol* (V), giving a Zerewitinoff value of one and, as expected, showing no appreciable absorption in the usual ultraviolet region.

 (V.)

 (VI.)

 (VII.)

Owing to its insolubility, no anionotropic rearrangement (Jones and McCombie, *J.*, 1943, 261 and following papers in this series) was observed on shaking with dilute sulphuric acid, but in aqueous alcoholic solution, 1% sulphuric acid was sufficient to give the rearranged *carbinol* (VI), the conjugated vinylacetylene system of which absorbed strongly at 2290 A.

A variety of methods was examined in attempts to dehydrate (VI) to the conjugated trienyne, including heating with potassium hydrogen sulphate and with *p*-toluenesulphonic acid in dioxan, pyrolysis of the *benzoate*, and treatment of the latter with dimethylaniline, but none gave satisfactory results. Either the carbinol was recovered unchanged or the product exhibited abnormal ultraviolet absorption. Accordingly the *chloro-compound* corresponding to (VI) was prepared by shaking an ethereal solution of the carbinol (V) with concentrated hydrochloric acid (cf. Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77). Treatment of this chloro-compound with diethylaniline at 150—160° yielded a *hydrocarbon*, $C_{20}H_{30}$, which absorbed five mols. of hydrogen on quantitative hydrogenation. The light absorption data for this compound, compared in Table I with those of somewhat related carbinols, etc., were at first not readily interpretable, but it was abundantly clear that the required fully conjugated trienyne, which would be expected to show maximal absorption at about 3000—3100 A., had not been produced. Indubitable evidence for the presence of the conjugated dienyne hydrocarbon (VII) in this product was provided by the isolation of *iso*geronic acid on

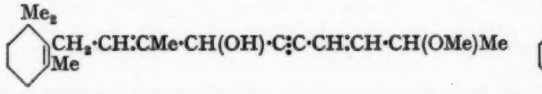
TABLE I.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Hydrocarbon (VII) (cf. (IX) in Table II)	2200	6,000	Deca-2 : 4 : 6 : 8-tetraen-1-ol [3]	2985	64,000
	2820	19,500		3110	64,000
	2900	19,500	Deca-2 : 4 : 6 : 8-tetraene [4]	2720	17,000
Deca-3 : 7-dien-5-yn-2 : 9-diol [1]	2650	21,500		2840	40,500
	2800	19,000		2960	58,500
Deca-3 : 5 : 7-trien-1-yn-9-ol [2]	2790	40,000		3200	58,500
	2920	60,000			
	3050	54,000			

[1] Heilbron, Jones, and Raphael, *J.*, 1943, 268. [2] Heilbron, Jones, and McCombie, *J.*, 1944, 134.
[3] Reichstein and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 1074. [4] Kuhn, *Angew. Chem.*, 1937, **50**, 705.

ozonolysis. The low yield of the latter (*ca.* 7%) does not compare unfavourably with that obtained from α-ionone itself (Lindenbaum, Andrews, and Young, *J. Amer. Chem. Soc.*, 1944, **66**, 2130) but it may indicate the presence of isomeric hydrocarbons.

Simultaneously with the investigations described above, the condensation of the C_{14} aldehyde (III) with 2-methoxyhex-3-en-5-yne was studied. The *methoxy-carbinol* (VIII), produced in excellent yield and showing light absorption corresponding to its conjugated vinylacetylene system, was smoothly isomerised in aqueous

(VIII.)  (IX.)

acetone containing 1% sulphuric acid to the rearranged *methoxy-carbinol* (IX; R = OH). Treatment of the parent compound (VIII) with concentrated hydrochloric acid similarly afforded the *chloro-compound* (IX; R = Cl). The structures of these two compounds (*i.e.*, IX; R = OH and Cl) follow from the methods of preparation, which have been investigated in detail in many analogous cases (see previous papers in this series), and their light absorption properties are practically identical (Table II). The maximal absorption is at somewhat longer wavelengths (*ca.* 150 A.) than has been observed with other conjugated dienyne systems, but these effects must obviously be attributed to the influence of substituent groups. It will be noted that this absorption is almost the same as that of the hydrocarbon (VII) (Table I) referred to above, thus providing additional evidence for the structure assigned to it. The carbinol (IX; R = OH) could not readily be dehydrated; it was recovered unchanged even after distillation at 220°/0·05 mm.

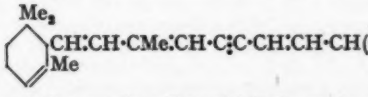
TABLE II.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Methoxy-carbinol (IX; R = OH)	2710	20,500	Methoxy-compound (X) (cf. Table I)	3160	29,000
	2780 *	20,000		3100 *	28,000
	2880 *	16,000	Vitamin A [1]	3280	51,000
Chloro-compound (IX; R = Cl)	2800	19,000	Methyl ether [2]	3150	33,750
	2900	17,500			

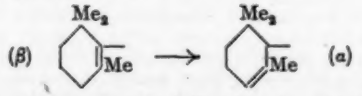
* Inflexion.

[1] Baxter and Robeson, *J. Amer. Chem. Soc.*, 1942, **64**, 2411. [2] Oroshnik, *ibid.*, 1945, **67**, 1627.

Treatment of the chloro-compound with diethylaniline at 115° was only partially effective in splitting out hydrogen chloride, but at 160° this process was complete. The resulting methyl ether proved to be highly unstable, distilling as a pale yellowish oil but becoming red extremely rapidly on exposure to air. Its light absorption data (Table II) and the isolation of *iso*geronic acid on ozonolysis indicated that once again the expected fully conjugated system had not been obtained and the final product can only be formulated as (X).

 (X.)

The explanation of this failure of the cyclic ethenoid linkage to participate in the conjugated system, as in the two examples quoted in this paper and as suggested in related earlier work (Heilbron, Jones, and Lacey, this vol., p. 27) is not clear. It has not been possible rigidly to prove that the original C_{14}-aldehyde actually contains a double bond in the β-ionone position, but the fact that a totally different isomeric aldehyde is produced when the synthesis is carried out with α-ionone must surely be regarded as strong indirect evidence. No isomerisation from the β- into the α-position, *i.e.*,



would be expected to occur during the Grignard condensation involved in the preparation of either (V) or (VIII), but the same cannot be said either of the hydrochloric acid treatment employed to prepare the rearranged chloro-compound in each case, or of the subsequent dehydrochlorination stage with diethylaniline.

Oroshnik (*J. Amer. Chem. Soc.*, 1945, **67**, 1627) has recently claimed to have synthesised vitamin A methyl ether by the condensation of the ethynylcarbinol from β-ionone with 1-chloro-4-methoxy-2-methylbut-2-ene ($CH_2Cl{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}OMe$), followed by semihydrogenation of the acetylenic bond, anionotropic rearrangement, and dehydration. It appears to us highly improbable that certain stages in the synthesis have proceeded in the manner claimed, and it may be noted that the final product, said to be vitamin A methyl ether, shows maximal absorption at 3150 A. This corresponds very closely to the absorption of the methyl ether (X) described above and it seems unlikely that the vitamin A chromophoric system is present in the final product. Had the author been able to provide evidence of the production of geronic acid on ozonolysis of the latter the claim might have been irrefutable, but since this is not the case, it can only be accepted with considerable reservations.

Experimental.

(Absorption spectra were determined in alcoholic solutions.)

3-(2′ : 6′ : 6′-*Trimethyl*cyclo*hexenyl*)-1-*methylcrotonaldehyde* (III).—Employing the method of Heilbron, Johnson, Jones, and Spinks (*J.*, 1942, 732) the action of sodium methoxide on a mixture of β-ionone (commercial, $n_D^{16°}$ 1·5156. Light absorption: Maxima, 2260 A., ε = 11,000; 2920 A., ε = 6,500) and ethyl chloroacetate in dry ether at − 60° gave the glycide ester (b. p. 110—130°/0·1 mm.) and then the glycide acid as a viscous reddish oil. The slow decarboxylation of the latter in the manner described (*loc. cit.*) yielded the aldehyde, b. p. 90—120°/0·01 mm., in 20% overall yield (calculated on β-ionone). Redistillation gave a pale yellowish oil, b. p. 105—106°/0·03 mm., 89—90°/0·01 mm., $n_D^{19°}$ 1·5118.

The redistilled aldehyde was treated with semicarbazide acetate in the normal manner, giving the *semicarbazone* which separated from aqueous methyl alcohol as plates, m. p. 148—150° (Found: N, 16·05. $C_{15}H_{25}ON_3$ requires N, 15·9%). Light absorption: Maxima, 2220 A., ε = 7,500; 2650 A., ε = 30,000.

The powdered semicarbazone (15 g., m. p. 147°) was stirred and refluxed with sulphuric acid (200 c.c., 15% w/v) in the presence of light petroleum (80 c.c., b. p. 80—100°) in nitrogen until two clear layers were obtained (4—5 hours). The aqueous portion was extracted with light petroleum and the combined petroleum layers washed and dried. Removal of solvent under reduced pressure in an atmosphere of nitrogen gave the aldehyde (11 g., 92%), b. p. 50° (bath temp.)/10^{-4} mm., $n_D^{19°}$ 1·5109, $n_D^{25°}$ 1·5094.

1-(2′ : 6′ : 6′-*Trimethyl*cyclo*hexenyl*)-3-*methyldec*-2-*en*-5-*yn*-4-*ol* (V).—To an ice-cold solution of hexynylmagnesium bromide (Cymerman, Heilbron, and Jones, *J.*, 1944, 146) prepared from 1-hexyne (5 g.) and ethylmagnesium bromide (from 1 g. of magnesium) in dry ether (150 c.c.) a solution of the β-ionone C_{14} aldehyde (3·5 g., $n_D^{25°}$ 1·5094, regenerated from the semicarbazone) in dry ether (50 c.c.) was added with stirring during 20 minutes. The mixture was stirred at 20° for 19 hours and then refluxed for a further 6 hours. Decomposition of the Grignard complex with saturated ammonium chloride solution and isolation of the product with ether gave the *carbinol* (4·5 g., 92%) as a colourless slightly viscous oil, b. p. 80—85° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5064 (Found: C, 83·6; H, 11·3. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%). Active hydrogen (Zerewitinoff): The carbinol (323 mg.) gave 25·2 c.c. of methane at 18°/763 mm. (0·95 active hydrogen atom per mol.). Light absorption: End absorption only, 2160 A., ε = 4,500. The carbinol failed to yield a solid derivative with α-naphthyl *iso*cyanate. The carbinol (0·5 g.) was heated with acetic anhydride (0·5 g.) and anhydrous potassium acetate at 120° for 1 hour in nitrogen. Water was added to the product which was neutralised with sodium bicarbonate. Isolation with ether gave the *acetyl* derivative as a pale yellow oil, b. p. 90° (bath temp.)/10^{-4} mm., $n_D^{20°}$ 1·4986 (Found: C, 79·8; H, 10·3. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·35%). Light absorption: End absorption only, 2200 A., ε = 5,000.

1-(2′ : 6′ : 6′-*Trimethyl*cyclo*hexenyl*)-3-*methyldec*-3-*en*-5-*yn*-2-*ol* (VI).—The above carbinol (5 g., $n_D^{18°}$ 1·5075) was dissolved in 80% aqueous alcohol containing 1% (w/v) of sulphuric acid, and the mixture was kept for 48 hours at 20°. The solution was poured into water and the product extracted with ether. Evaporation of the washed and dried extracts gave 1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldec*-3-*en*-5-*yn*-2-*ol* (4·7 g., 94%) as a pale yellow viscous oil, b. p. 85—90° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·5124 (Found: C, 82·95; H, 11·1. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%). Light absorption: Maximum, 2290 A., ε = 16,500. Active hydrogen (Zerewitinoff): The carbinol (176 mg.) gave 13·6 c.c. of methane at 25°/768 mm. (0·9 active hydrogen atom per mol.). The carbinol failed to yield a solid α-naphthylurethane. The carbinol (1·0 g.) in dry pyridine (10 c.c.) was treated with benzoyl chloride (0·6 g., redistilled), the mixture was kept for 24 hours at 20° in nitrogen, after which it was poured into water and extracted with ether. Evaporation of the washed and dried extract and distillation of the residue gave two fractions: (a) b. p. 90—100° (bath temp.)/10^{-4} mm. (0·2 g.), $n_D^{18°}$ 1·5255, consisting of a mixture with unchanged carbinol, and (b) b. p. 100—110° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·5360, the *benzoate* (0·6 g.), a yellow viscous oil (Found: C, 82·8; H, 9·1. $C_{27}H_{35}O_2$ requires C, 82·6; H, 9·25%). Light absorption: Maximum, 2290 A., ε = 35,000.

1-(2′ : 6′ : 6′-*Trimethyl*cyclo*hexanyl*)-3-*methyldecan*-2-*ol*.—1-(2′ : 6′ : 6′-Trimethyl*cyclo*hexenyl)-3-methyldec-3-en-5-yn-2-ol (0·44 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen in the presence of platinic oxide (0·1 g.) until absorption ceased. The carbinol required 135 c.c. of hydrogen (I = 3·75). Removal of catalyst and distillation of the residue afforded 1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexanyl*)-3-*methyldecan*-2-*ol* (0·3 g., 67%) as a slightly viscous, colourless oil, b. p. 80° (bath temp.)/10^{-4} mm., $n_D^{20°}$ 1·4750 (Found: C, 80·8; H, 13·3. $C_{20}H_{40}O$ requires C, 81·0; H, 13·6%).

2-*Chloro*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldec*-3-*en*-5-*yne*.—1-(2′ : 6′ : 6′-Trimethyl*cyclo*hexenyl)-3-methyldec-2-en-5-yn-4-ol (V) (2·5 g.) in ether (3 c.c.) was shaken with concentrated hydrochloric acid (10 c.c.) in nitrogen for 2 hours at 20°. The mixture was poured into water and the product isolated with ether. Removal of solvent from the washed and dried extract gave the *chloro-compound* (2·35 g., 85%) as a pale yellow oil, b. p. 65—70° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5210 (Found: C, 78·4; H, 10·15. $C_{20}H_{31}Cl$ requires C, 78·25; H, 10·2%). Light absorption: Maxima, 2390 A., ε = 17,000; 2420 A., ε = 17,000; 2810 A., ε = 4,500; 2900 A., ε = 4,000.

1-(2′ : 6′ : 6′-*Trimethyl*-$\Delta^{2'}$-cyclo*hexenyl*)-3-*methyldeca*-1 : 3-*dien*-5-*yne* (VII).—The above chloro-compound (1·2 g.) was heated with diethylaniline (20 c.c., redistilled) at 150—160° for 3 hours in nitrogen. A copious crystalline precipitate of diethylaniline hydrochloride separated on cooling. The bulk of the excess of diethylaniline was removed at 100°/4 mm., and the residue treated with ether and 2N-sodium hydroxide solution. The ethereal layer was washed with sodium hydroxide solution and the combined aqueous layers acidified with concentrated nitric acid and treated with an excess of 5% silver nitrate solution, giving a precipitate of silver chloride which after washing and drying at 100° weighed 0·55 g. (98% of theory). The ethereal extract was washed with 2N-hydrochloric acid, sodium bicarbonate solution, and water. Removal of solvent from the dried extract afforded 1-(2′ : 6′ : 6′-*trimethyl*-$\Delta^{2'}$-cyclo*hexenyl*)-3-*methyldeca*-1 : 3-*dien*-5-*yne* (0·9 g., 84%) as a pale yellow mobile oil, b. p. 70—75° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5466 (Found: C, 88·7; H, 11·2. $C_{30}H_{30}$ requires C, 88·8; H, 11·2%). On treatment with antimony trichloride in chloroform the hydrocarbon gave a purple colour changing to a deep blue.

Ozonolysis of 1-(2′ : 6′ : 6′-*Trimethyl*-$\Delta^{2'}$-cyclo*hexenyl*)-3-*methyldeca*-1 : 3-*dien*-5-*yne* (VII).—A solution of the hydrocarbon (1·7 g.) in dry carbon tetrachloride (40 c.c.) was treated with a slow stream of ozonised oxygen and the product isolated with ether as outlined by Heilbron, Johnson, and Jones (*J.*, 1939, 1560). Evaporation of the ethereal extracts gave an oil which was extracted with hot water (10 c.c.), and the filtered aqueous extract treated with an alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate. Crystallisation of the solid (150 mg.) so obtained, from methyl alcohol gave the 2 : 4-dinitrophenylhydrazone of *iso*geronic acid, m. p. 141°, undepressed on admixture with an authentic specimen (m. p. 140°). With the corresponding derivative of geronic acid a 20° depression in m. p. was observed.

9-*Methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldeca*-2 : 7-*dien*-5-*yn*-4-*ol* (VIII).—A solution of 2-methoxyhex-3-en-5-yne (6 g., Heilbron, Jones, and Weedon, *J.*, 1945, 82) in dry ether (100 c.c.) was added to an ethereal solution of ethylmagnesium bromide (from 1·2 g. of magnesium) and the mixture was refluxed for 2·5 hours in nitrogen. A solution of the β-ionone C_{14} aldehyde (5·15 g., regenerated from the semicarbazone) in ether (100 c.c.) was added to the ice-cold Grignard solution during 1·5 hours and the mixture was then refluxed for 3 hours and stirred for a further 16 hours in nitrogen. Isolation by the usual method gave two fractions: (a) recovered aldehyde (1·2 g., 23%), b. p. 50° (bath temp.)/10^{-4} mm.; (b) 9-*methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldeca*-2 : 7-*dien*-5-*yn*-4-*ol* (5·7 g., 94% yield calculated on reacted aldehyde), b. p. 94—98° (bath temp.)/10^{-4} mm., as a colourless liquid, $n_D^{17°}$ 1·5300 (Found: C, 80·05; H, 10·2; $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%). Active hydrogen (Zerewitinoff): The carbinol (131 mg.) gave 10·1 c.c. of methane at 20°/759·5 mm. (1·0 active hydrogen atom per mol.). Light absorption: Maxima, 2235 and 2270 A., ε = 16,000 in each case. Inflexion, 2350 A., ε = 13,500.

9-*Methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldeca*-3 : 7-*dien*-5-*yn*-2-*ol* (IX; R = OH).—The above methoxy-carbinol (VIII) (4 g.) was dissolved in sulphuric acid (500 c.c.; 1% w/v) containing acetone (250 c.c.) and the clear solution allowed to stand for 7 days at 20°. After pouring into water (5 l.), the product was isolated with ether. Evaporation of the washed and dried extract gave 9-*methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldeca*-3 : 7-*dien*-5-*yn*-2-*ol* (3 g., 75%) as a colourless viscous liquid, b. p. 104—105° (bath temp.)/10^{-4} mm.; $n_D^{18°}$ 1·5492 (Found: C, 79·85; H, 10·05. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%). Active hydrogen (Zerewitinoff): The carbinol (132 mg.) gave 9·4 c.c. of methane at 16°/769 mm. (0·95 active hydrogen atom per mol.).

2-*Chloro*-9-*methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3-*methyldeca*-3 : 7-*dien*-5-*yne* (IX; R = Cl).—A solution of the unrearranged methoxy-carbinol (2·5 g.) in ether (7 c.c.) was shaken with concentrated hydrochloric acid (15 c.c.) for 3 hours at 20° in nitrogen. The yellow emulsion was poured into water and extracted thoroughly with ether. Removal of solvent from the washed and dried extract afforded the *chloro-compound* (2·4 g., 90%) as a pale yellow mobile oil, b. p. 65—66° (bath temp.)/10^{-4} mm., $n_D^{17°}$ 1·5580 (Found: C, 75·55; H, 9·6. $C_{21}H_{31}OCl$ requires C, 75·3; H, 9·35%).

9-*Methoxy*-1-(2′ : 6′ : 6′-*trimethyl*-$\Delta^{2'}$-cyclo*hexenyl*)-3-*methyldeca*-1 : 3 : 7-*trien*-5-*yne* (X).—The chloro-compound (2 g.) was heated with diethylaniline (20 c.c., redistilled) for 3 hours at 160° in nitrogen. The cooled solution was diluted with ether and rapidly shaken several times with 2N-nitric acid to remove basic material. Addition of excess of 5% silver nitrate solution to the aqueous layers gave a precipitate of silver chloride which after washing and drying at 100° weighed 0·8 g. (93% of theory). The ethereal extract was washed and dried and on distillation gave the *methoxy-polyenyne* as a readily oxidised pale yellow oil (1·45 g., 81%), b. p. 95—96° (bath temp.)/10^{-4} mm., $n_D^{16°}$ 1·5860 (Found: C, 80·3, 80·65, 81·0, 81·7; H, 9·65, 9·75, 9·95, 10·3. $C_{21}H_{30}O$ requires C, 84·5; H, 10·15%).

Ozonolysis of (X).—A solution of the methoxy-polyenyne (0·3 g.) in carbon tetrachloride (10 c.c.) was treated with ozonised oxygen for 7 hours; glacial acetic acid (10 c.c.) was then added and ozonolysis continued for a further 17 hours. Water (25 c.c.) and hydrogen peroxide (1 c.c. of 100-volume solution) were added to the product and the mixture was heated on the steam-bath for an hour under reflux. Water and acetic acid were distilled off under reduced pressure, and the product isolated with ether (Heilbron, Johnson, and Jones, *J.*, 1939, 1560). Evaporation of the ethereal extracts gave an oil which on treatment with 2 : 4-dinitrophenylhydrazine sulphate yielded an orange solid (120 mg., 35% of theory). Crystallisation from aqueous acetic acid gave orange micro-crystals of *iso*geronic acid 2 : 4-dinitrophenylhydrazone, m. p. 139—140°, undepressed on admixture with an authentic sample, but depressed by 26° when mixed with geronic acid 2 : 4-dinitrophenylhydrazone (m. p. 135°).

The authors are indebted to Dr. E. A. Braude for the spectrographic data and to the Rockefeller Foundation for financial assistance which rendered this work possible.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7. [*Received, November 29th*, 1945.]

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99. *Researches on Acetylenic Compounds. Part V.* αβ-*Acetylenic Hydroxy-acids.*

By L. J. HAYNES and E. R. H. JONES.

Carboxylation of ethynylcarbinols [*e.g.*, –CH(OH)·C≡CH], by treating the Grignard complexes with solid carbon dioxide in an autoclave, gives excellent yields of the αβ-acetylenic hydroxy-acids (*e.g.*, I—IV). The choice of solvent is important as the solubility of the initial Grignard complex has considerable influence upon the yield of acid. Decarboxylation and esterification as well as the ultraviolet light absorption properties of the acids have been studied.

When the above procedure is applied to the vinylacetylenic carbinol, hex-3-en-5-yn-2-ol, a furanacetic acid is formed together with the expected carboxylation product. This intramolecular hydration is analogous to that observed when the carbinol itself is treated with acids in the presence of mercuric salts.

αβ-ACETYLENIC carboxylic acids can generally be obtained readily by reaction of the Grignard complexes or sodio-derivatives of acetylenic hydrocarbons with carbon dioxide, ethyl carbonate, or ethyl chloroformate. The carboxylation of ethynylcarbinols, however, appears to have presented considerable difficulty to previous

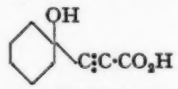
$$R{\cdot}C{\equiv}CH \longrightarrow R{\cdot}C{\equiv}C{\cdot}CO_2H$$

workers. Lespieau and Viguier (*Compt. rend.*, 1908, **146**, 295; see also Lespieau, *Ann. Chim.*, 1912, **27**, 178, 184) described carboxylations of the Grignard complexes from propargyl alcohol and ethylethynylcarbinol, but no yields were stated, and the authors noted that absorption of carbon dioxide was very slow and recommended the passage of gas for periods of up to a fortnight. Salkind and Michantjev (*J. Gen. Chem. Russia*,

1941, **11**, 92) obtained only a 1·25% yield of the acid (I; $R_1 = R_2 = Me$) on carboxylation of the Grignard complex from dimethylethynylcarbinol and state that this can be improved somewhat by passing in carbon dioxide for five days. In connection with the synthesis of the selective growth inhibitor, δ-hexenolactone (Haynes and Jones, *Nature*, 1945, **155**, 730), and related substances, a detailed study of the carboxylation of ethynylcarbinols has been undertaken.

In the above mentioned investigations the reactions were presumably attempted in ethereal solutions. It has now been found that the choice of solvent for these carboxylations is extremely important, as the Grignard complexes from simple ethynylcarbinols are only very sparingly soluble in ether. Benzene has proved to be a useful solvent for this purpose and, by carboxylating under pressure in the presence of an excess of solid carbon dioxide at ordinary temperatures for twenty-four hours, excellent conversions (up to 70%) of the carbinols and yields (usually 80—90%) of the acetylenic hydroxy-acids (I—IV) have been obtained. (The comparatively simple experimental procedure is described in detail below.) By this means methyl-, propyl-, and dimethyl-ethynylcarbinols have been converted into the *acids* (I; $R_1 = H$; $R_2 = Me$), (I; $R_1 = H$; $R_2 = Pr$), and (I; $R_1 = R_2 = Me$); pent-1-yn-4-ol gave (II) (Haynes and Jones, *loc. cit.*), and

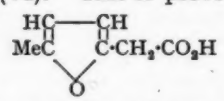
(I.) $CR_1R_2(OH)\cdot C{:}C\cdot CO_2H$ $\quad$ $CHMe(OH)\cdot CH_2\cdot C{:}C\cdot CO_2H$ (II.)

(III.) 

$CHMe(OH)\cdot CH{:}CH\cdot C{:}C\cdot CO_2H$ (IV.)

ethynyl*cyclo*hexanol gave the highly crystalline *acid* (III) in excellent yield.* From hex-3-en-5-yn-2-ol (Jones and McCombie, *J.*, 1943, 261) two isomeric acids were obtained, that produced in greater yield being proved to be *hex-3-en-1-yn-5-ol-1-carboxylic acid* (IV) by its light absorption properties and conversion into 4-aceto-*n*-valeric acid.

The by-product formed during the carboxylation of hex-3-en-5-yn-2-ol, and accompanying the vinylacetylenic hydroxy-acid (IV), is 5-methylfuran-2-acetic acid (VI). This is proved by its m. p., its light

(V.) $CHMe\cdot CH{:}CH\cdot C{:}CH\cdot CO_2H$ (O-bridge) $\quad$  (VI.)

absorption properties, and the formation of 2 : 5-dimethylfuran on decarboxylation. The intramolecular hydration by which this acid is formed is exactly analogous to that leading to 2 : 5-dimethylfuran on hydration of hex-3-en-5-yn-2-ol with dilute acids in the presence of mercuric salts (Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54), an intermediate stage such as (V) probably being involved. Whether this hydration occurs during the actual carboxylation reaction or on the subsequent treatment of the magnesium complex with acids has yet to be determined. It may well be that the difficulty we have experienced in isolating any homogeneous product from the carboxylation of propenylethynylcarbinol is associated with complications due to simultaneous hydration and rearrangement reactions.

A comparison, using hexynylmagnesium bromide, of the yields accruing with the carbon dioxide, ethyl carbonate, and ethyl chloroformate processes for the introduction of the carboxylic acid group, reveals the superiority, in this respect, of the straightforward carboxylation reaction.

The αβ-acetylenic hydroxy-acids are crystalline solids which are stable, but decompose above their melting points. With traces of copper bronze at about 200° quantitative decarboxylation into the parent ethynylcarbinols takes place. The acids can be characterised very conveniently as their S-*benzylisothiouronium* salts, and the *ethyl* esters are readily produced in excellent yields by refluxing with alcoholic sulphuric acid. Treatment of the resulting esters [except the ester of (III)] with aqueous ammonia gives non-crystalline products, doubtless due to addition to the acetylenic bond (cf. Feist, *Annalen*, 1906, **345**, 100).

Light absorption data for the acids and their esters in alcoholic solutions are given in the accompanying table. As in the corresponding αβ-ethylenic acids, the maximal absorption is just beyond the limit of the usual ultraviolet range, and consequently only the intensities at convenient wavelengths are recorded.

	Acid.		Ethyl ester.			Acid.		Ethyl ester.	
	λ, A.	ε.	λ, A.	ε.		λ, A.	ε.	λ, A.	ε.
(I; $R_1 = H$; $R_2 = Me$)	2110	4,500	—	—	$Bu\cdot C{:}C\cdot CO_2H$	2140	6,500	2150	5,000
(I; $R_1 = H$; $R_2 = Pr$)...	2150	4,500	2140‡	5,000	Cf. Crotonic acid [1]	2040*	11,500	—	—
(I; $R_1 = R_2 = Me$)	2150	4,000	2150	4,500	(IV)	2455*	12,000	—	—
(II)	2150	4,000	2160	6,000		2560†	9,500	2480*	14,000
(III)	2150	4,500	2160	7,000	Cf. Sorbic acid	2540*	24,800	—	—

* Maximum. † Inflexion. ‡ Methyl ester. [1] Smakula, *Angew. Chem.*, 1934, **47**, 657.

Experimental.

(Light absorption data obtained with alcoholic solutions.)

Hex-1-yn-1-carboxylic Acid.—A solution of 1-hexyne (24 g.) in ether (25 c.c.) was added to an ethereal solution of ethylmagnesium bromide (from 6 g. of magnesium) and the mixture refluxed for 4 hours. The solution of the Grignard

* Hydrogenation of the acid (III) to the *spiro*-lactone, followed by dehydration and cyclisation of the acid chloride, appears to furnish a convenient route to 1-hydrindenone and related substances (cf. Chuang, Tien, and Ma, *Ber.*, 1936, **69**, 1494; Haberland and Heinrich, *ibid.*, 1939, **72**, 1222).

complex was cooled and poured on to a large excess (*ca.* 200 g.) of solid carbon dioxide in a steel autoclave of capacity *ca.* 1 l. The autoclave was sealed, shaken at room temperature for 24 hours, and then allowed to stand for 48 hours. Excess pressure was then released and the white powdery complex transferred to a beaker and treated with ice and 2N-sulphuric acid (*ca.* 500 c.c.). After the initial vigorous effervescence had subsided, isolation with ether in the usual manner gave hex-1-yn-1-carboxylic acid (24·9 g.; 72%), b. p. 128°/12 mm., 93°/3 mm., $n_D^{16°}$ 1·4633 (Zoss and Hennion, *J. Amer. Chem. Soc.*, 1941, **63**, 1152, give b. p. 122°/10 mm., $n_D^{20°}$ 1·4619).

Ethyl Hex-1-yn-1-carboxylate.—(a) A solution of 1-hexynylmagnesium bromide (prepared as above, from 6 g. of magnesium) in benzene–ether (300 c.c.; 1 : 1) was added dropwise during 6 hours to a vigorously stirred, gently refluxing, solution of ethyl carbonate (40 g.) in ether (150 c.c.) in nitrogen. As the addition proceeded, a white crystalline solid separated and the solution assumed a dark brown colour. The reaction mixture was stirred overnight at 20° and the unreacted Grignard complex decomposed with ammonium chloride solution (ice). Isolation by the normal procedure gave ethyl hex-1-yn-1-carboxylate (14·6 g.), b. p. 105—106°/16 mm., $n_D^{14°}$ 1·4491 (Moureau and Delange, *Bull. Soc. chim.*, 1903, **29**, 653 give b. p. 106—108°/24 mm.).

(b) A solution of 1-hexynylmagnesium bromide (from 6 g. of magnesium) in benzene–ether (300 c.c.; 1 : 1) was added dropwise during 3½ hours to a vigorously stirred solution of ethyl chloroformate (35 g.) in ether (*ca.* 200 c.c.) at 20° in nitrogen. A white precipitate formed as the addition proceeded. The unreacted Grignard complex was decomposed with ammonium chloride solution (ice); isolation with ether gave ethyl hex-1-yn-1-carboxylate (10·1 g.), b. p. 103—105°/18 mm., $n_D^{15°}$ 1·4483, and *ca.* 2 g. of ethyl carbamate, b. p. 85°/18 mm., m. p. 49—50°, undepressed on admixture with an authentic specimen.

Identical amides were obtained from each specimen of ester on shaking overnight at 20° with ammonia (*d* 0·88). They separated from light petroleum (b. p. 60—80°) in leaflets, m. p. 68—69°, undepressed on admixture with each other (Zoss and Hennion, *loc. cit.*, give m. p. 68—69°).

Carboxylation of Ethynylcarbinols. General Method.—Ethylmagnesium bromide (from 1 g.-mol. of magnesium) was prepared in ethereal solution in the usual way, and the excess of ether evaporated during the addition of sodium dried AnalaR benzene (200 c.c.). The ethynylcarbinol (½ g.-mol.) in benzene (100 c.c.) was added to the ice-cooled solution during 1½ hours and the mixture refluxed for 2 hours. The solution of the Grignard complex was poured on to a large excess (*ca.* 200 g.) of solid carbon dioxide in a steel autoclave, capacity *ca.* 1 l., which was then sealed and shaken at room temperature for 24 hours. The resulting complex was hydrolysed with ice and a 20% excess of the calculated quantity of 15% sulphuric acid at 0°. After the initial vigorous effervescence had subsided, the aqueous solution was saturated with salt and extracted with ether. The ethereal extract was washed thoroughly with saturated sodium bicarbonate solution. After extraction of any non-acid material with ether, the bicarbonate washings were acidified with 15% sulphuric acid, saturated with salt, and extracted with ether. Owing to the great solubility of the lower molecular weight acids in water, extractions in these cases were carried out in a continuous extraction apparatus. Evaporation of the ethereal solution after drying (sodium sulphate), gave the acetylenic hydroxy-acid, generally as a syrupy liquid which solidified completely on standing at 0° for some hours. Unchanged carbinol was recovered on distillation of the residue remaining after evaporation (through a 12 inch Dufton column) of the residual ethereal solution from the sodium bicarbonate washing.

β-(1′-Hydroxy-1′-cyclohexyl)propiolic Acid (III).—From 1-ethynylcyclohexanol (½ g.-mol.; prepared by the method detailed by Heilbron, Jones, and Weedon, *J.*, 1945, 81, for propenylethynylcarbinol). The Grignard complex was prepared in ether (250 c.c.) in which it was completely soluble. The *acid* (30 g.; 72% conversion; 9 g. of carbinol recovered) readily solidified on cooling and crystallised from benzene–ethyl acetate in plates, m. p. 125° (Found: C, 64·35; H, 7·25. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). A mixture of the acid (1 g.) and copper bronze (10 mg.) was heated at 200°/20 mm. Ethynylcyclohexanol (0·5 g.) distilled, having $n_D^{19°}$ 1·4818 and m. p. 28°, undepressed on admixture with an authentic specimen. The acid (5 g.) was refluxed for 16 hours with alcoholic sulphuric acid (1%; 25 c.c.); isolation by the usual procedure gave *ethyl β-(1′-hydroxy-1′-cyclohexyl)propiolate* (5 g.), as a viscous odourless liquid, b. p. 93°/2 mm., $n_D^{20°}$ 1·4910 (Found: C, 67·35; H, 8·45. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). The ester (0·5 g.) was hydrolysed on standing with alcoholic potassium hydroxide (50 c.c.; 2%) for 28 hours. Isolation by the usual procedure gave the acid (0·3 g.) which did not depress the m. p. of an authentic sample. The ester (1 g.) was shaken overnight at 20° with ammonia (*d* 0·88; *ca.* 10 c.c.); it dissolved completely and, on scratching, the solution deposited needles of the *amide* (0·8 g.), m. p. 157°, after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) or water (Found: C, 64·75; H, 7·95. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·85%). Light absorption: Maximum, 2150 A.; ε = 7,500.

Pent-1-yn-4-ol-1-carboxylic Acid (II).—Pent-1-yn-4-ol (42 g.; Kreimeier, U.S.P. 2,106,182) was carboxylated by the general method to give *pent-1-yn-4-ol-1-carboxylic acid* (40 g.; 62·5% conversion, 6·7 g. carbinol recovered) as a very hygroscopic, crystalline solid. The acid, sublimed at 50° (bath temp.)/10^{-4} mm., had m. p. 59° (Found: C, 56·55; H, 6·2. $C_6H_8O_3$ requires C, 56·25; H, 6·3%). The *p-bromophenacyl* ester separated from aqueous alcohol as lustrous plates, m. p. 78—80° (Found: C, 51·6; H, 4·0. $C_{14}H_{13}O_4Br$ requires C, 51·7; H, 4·05%). The *S-benzylisothiouronium* salt crystallised from alcohol in micro-laths, m. p. 157° (decomp.) (Found: C, 57·4; H, 6·35. $C_{14}H_{18}O_3N_2S$ requires C, 57·1; H, 6·15%). The *ethyl* ester prepared as above had b. p. 90°/0·2 mm., $n_D^{19°}$ 1·4660 (Found: C, 61·7; H, 8·1. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%). A solution of the acid (1 g.) in methyl acetate (35 c.c.) was shaken with hydrogen in presence of platinic oxide until absorption of hydrogen was complete. The δ-hexolactone obtained on removal of catalyst and solvent had $n_D^{18·5°}$ 1·4448 (Linstead and Rydon, *J.*, 1934, 2000, give $n_D^{20°}$ 1·4451). The *S-benzylisothiouronium* salt of the corresponding hydroxy-acid separated from acetone in leaflets, m. p. 128—129° (Found: C, 56·4; H, 7·65. $C_{14}H_{22}O_3N_2S$ requires C, 56·35; H, 7·45%).

3-Methylbut-1-yn-3-ol-1-carboxylic Acid (I; $R_1 = R_2 = Me$).—This was prepared from dimethylethynylcarbinol (42 g.; Macullum, U.S.P. 2,125,384) by the general method. *3-Methylbut-1-yn-3-ol-1-carboxylic acid* (28·7 g.; 45% conversion) was obtained as a hygroscopic solid; sublimed at 50° (bath temp.)/10^{-4} mm., it had m. p. 90° (Found: C, 56·1; H, 6·1. $C_6H_8O_3$ requires C, 56·25; H, 6·3%). (Salkind and Michantjev, *loc. cit.*, describe this acid as a yellow oil.) The *S-benzylisothiouronium* salt crystallised from alcohol–light petroleum (b. p. 60—80°) in prisms, m. p. 167° (decomp.) (Found: C, 57·35; H, 6·25. $C_{14}H_{18}O_3N_2S$ requires C, 57·15; H, 6·15%). The *ethyl* ester prepared as above had b. p. 82°/0·5 mm., $n_D^{19°}$ 1·4560 (Found: C, 61·3; H, 7·8. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%).

But-1-yn-3-ol-1-carboxylic Acid (I; $R_1 = H$; $R_2 = Me$).—Prepared from methylethynylcarbinol (35 g.; Macullum, *loc. cit.*) by the general method, the Grignard complex separating from the benzene solution as a sticky solid. *But-1-yn-3-ol-1-carboxylic acid* (23 g.; 40% conversion) was obtained as a crystalline solid, subliming at 55° (bath temp.)/10^{-4} mm., m. p. 66—67° (Found: C, 52·5; H, 5·35. $C_5H_6O_3$ requires C, 52·65; H, 5·3%). The *S-benzylisothiouronium* salt separated from alcohol–light petroleum (b. p. 60—80°) in needle-like plates, m. p. 136·5° (decomp.) (Found: C, 55·8; H, 5·9. $C_{13}H_{16}O_3N_2S$ requires C, 55·7; H, 5·75%).

Hex-1-yn-3-ol-1-carboxylic Acid (I; $R_1 = H$; $R_2 = Pr$).—Prepared from propylethynylcarbinol (24·5 g.; Bowden, Heilbron, Jones, and Weedon, this vol., p. 39) by the general method. The *acid* (17 g.; 48% conversion, 9·5 g. carbinol recovered) was obtained as a crystalline solid, subliming at 55° (bath temp.)/10^{-4} mm., m. p. 64° (Found: C, 59·45. H, 7·1. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%). By carboxylating for 72 hours the conversion is increased to 66%.

The acid (1 g.) was heated to 170° in the presence of copper bronze (*ca.* 10 mg.). Propylethynylcarbinol (0·6 g.), $n_D^{19°}$ 1·4347 distilled rapidly. Its *α-naphthylurethane* separated from light petroleum (b. p. 60—80°) in prisms, m. p. 76°, undepressed on admixture with a specimen prepared from authentic carbinol (Found: N, 5·2. $C_{17}H_{17}O_2N$ requires N, 5·25%). The acid (10 g.) was refluxed with methyl-alcoholic sulphuric acid (100 c.c., 1%) for 24 hours in nitrogen. The resulting *methyl* ester (8·1 g.) had b. p. 135°/13 mm., 73°/0·2 mm., $n_D^{18·5°}$ 1·4618 (Found: C, 61·4; H, 8·05. $C_8H_{12}O_3$ requires C, 61·55; H, 7·75%).

Hex-3-en-1-yn-5-ol-1-carboxylic Acid (IV).—Prepared from hex-3-en-5-yn-2-ol (24 g.; Heilbron, Jones, Smith, and Weedon, *loc. cit.*) by the general method. The acidic product (19·5 g., 55% conversion), a dark brown oil, solidified completely on standing at 0°. Sublimation at 45—50° (bath temp.)/10^{-4} mm. gave two fractions: (i) 5-Methylfuran-2-acetic acid, more volatile, well formed prisms (*ca.* 4 g.), m. p. 61° (Found: C, 59·85; H, 5·7. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·75%). Light absorption: Maximum, 2210 A.; $\varepsilon = 7{,}500$ (Reichstein and Zschokke, *Helv. Chim. Acta*, 1932, **15**, 249, give m. p. 61—62°; Scott and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 2549, give m. p. 57—58°). The acid (0·25 g.) was heated to 250° in the presence of copper bronze (*ca.* 5 mg.). 2 : 5-Dimethylfuran (0·15 g.) distilled as a colourless liquid, $n_D^{19°}$ 1·4422. Light absorption: Maximum, 2200 A.; $\varepsilon = 8000$ (Heilbron, Jones, Smith, and Weedon, *loc. cit.*, give $n_D^{19°}$ 1·4424). Its maleic anhydride adduct had m. p. 73°, undepressed on admixture with an authentic sample (Heilbron *et al.*, *loc. cit.*, give m. p. 73°). Treatment with 2 : 4-dinitrophenylhydrazine reagent gave the bis-2 : 4-dinitrophenylhydrazone of acetonylacetone, m. p. 257° (decomp.) undepressed on admixture with an authentic specimen. Light absorption: Maxima, 2550, 3560, 3610 A.; $\varepsilon = 18{,}000$, 29,000, 29,000. Inflexion, 2800 A.; $\varepsilon = 14{,}500$ (cf. Braude and Jones, *J.*, 1945, 500). (ii) *Hex-3-en-1-yn-5-ol-1-carboxylic acid* (*ca.* 11 g.) as a less volatile, crystalline solid, m. p. 88° (Found: C, 59·6; H, 5·7. $C_7H_8O_3$ requires C, 60·0; H, 5·75%). When the acid (0·5 g.) was heated to 200° in the presence of copper bronze (*ca.* 10 mg.) hex-3-en-5-yn-2-ol (0·25 g.) distilled as a pale yellow liquid, $n_D^{19°}$ 1·4823 (Heilbron, Jones, Smith, and Weedon, *loc. cit.*, give $n_D^{18·5°}$ 1·4842). The phenylurethane separated from light petroleum (b. p. 60—80°) in plates, m. p. 83—84°, undepressed on admixture with an authentic specimen. Esterification of 2 g. of the acid (ii) with alcoholic sulphuric acid gave the *ethyl* ester (2 g.), b. p. 50° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·5076 (Found: C, 64·35; H, 7·6. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%).

4-Aceto-n-valeric Acid.—A solution of hex-3-en-1-yn-5-ol-1-carboxylic acid (2 g.) in methyl acetate (35 c.c.) was shaken with hydrogen in the presence of platinic oxide (100 mg.) until absorption was complete. The crude hydroxy-acid was oxidised with chromic acid and the semicarbazone of the 4-aceto-*n*-valeric acid so obtained had m. p. 145° (Ciamician and Silber, *Ber.*, 1913, **46**, 3077, give m. p. 147°; Blaise and Kohler, *Bull. Soc. chim.*, 1910, **7**, 222, give m. p. 144°). Hydrogenation of the ethyl ester (0·7 g.) described above, followed by oxidation, gave ethyl 4-aceto-*n*-valerate, the semicarbazone (0·6 g.) of which had m. p. 110° (Found: N, 17·95. Calc. for $C_{10}H_{19}O_3N_3$: N, 18·1%) (Blaise and Kohler, *loc. cit.*, give m. p. 107°).

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100. *The Constitution of Damson Gum. Part III. Hydrolysis Products from Methylated Damson Gum.*

By E. L. Hirst and J. K. N. Jones.

Damson gum has been converted into its fully methylated derivative, which on hydrolysis gives 2 : 3 : 5-trimethyl *l*-arabinose (8 parts), 2 : 3-dimethyl *l*-arabinose (4 parts), 2 : 4 : 6-trimethyl *d*-galactose (3 parts), 2 : 4-dimethyl *d*-galactose (3 parts), 4(?)-methyl *d*-galactose (1 part), 2-methyl *d*-galactose (1 part), 2 : 3 : 4-trimethyl *d*-glycuronic acid (2 parts), and 2 : 3-dimethyl *d*-glycuronic acid (2 parts), in the approximate proportions indicated, together with unidentified derivatives of *d*-mannose and *d*-xylose.

It has been shown (Hirst and Jones, *J.*, 1938, 1174) that damson gum contains the following sugars in the proportions indicated: *d*-glycuronic acid (1 part), *d*-mannose (1 part), *d*-galactose (2 parts), *l*-arabinose (3 parts), and *d*-xylose (*ca.* 2%). The polysaccharide has now been converted into a homogeneous fully methylated derivative by the use of the thallium hydroxide method of methylation (compare Hirst and Jones, *J.*, 1938, 502).

Methylated damson gum underwent partial cleavage on boiling with 1% methyl alcoholic hydrogen chloride giving a material of lower molecular weight which, like part of the degraded methylated damson gum molecule (Hirst and Jones, *J.*, 1939, 1939, 1482), could be hydrolysed with difficulty on treatment with hot N-hydrochloric acid followed by boiling with 5% methyl alcoholic hydrogen chloride. Eight different sugar derivatives were recognised as hydrolysis products, namely, 2 : 3 : 5-trimethyl *l*-arabinose, 2 : 3-dimethyl *l*-arabinose, 2 : 4 : 6-trimethyl *d*-galactose, 2 : 4-dimethyl *d*-galactose, 2-methyl *d*-galactose, 4(?)-methyl *d*-galactose, 2 : 3 : 4-trimethyl *d*-glycuronic acid, and 2 : 3-dimethyl *d*-glycuronic acid. Derivatives of *d*-mannose and *d*-xylose must also be present, but the identity of these sugar derivatives is as yet uncertain.

In our earlier paper it was stated that the dimethyl galactose isolated from the hydrolysis of the methylated degraded gum was 4 : 6-dimethyl *d*-galactose. It has now been established beyond doubt that the major portion of the dimethyl *d*-galactose present in the hydrolysis products of methylated degraded damson gum and of methylated damson gum itself is in fact 2 : 4-dimethyl *d*-galactose (I) (Hirst, *J.*, 1942, 76). The melting points of 2 : 4-dimethyl α- and β-methylgalactosides and of the sugar anilide have been compared and found to be identical with authentic samples (kindly supplied by Dr. F. Smith of Birmingham University and by Dr. D. J. Bell of Cambridge University). In addition a sample of the amide of 2 : 4-dimethyl *d*-galactonic acid gave no depression on admixture with the amide prepared from an authentic sample of the sugar isolated

from damson gum. In contrast, the melting point of 4 : 6-dimethyl *d*-galactose (Bacon, Bell, and Lorber, *J.*, 1940, 147) was depressed on admixture with a specimen of our 2 : 4-dimethyl *d*-galactose. An independent proof of the structure of the 2 : 4-dimethyl *d*-galactose has been arrived at from a study of its degradation with periodic acid, which oxidised it to formaldehyde (II) and to αα′-dimethoxy-*l*-araboglutardialdehyde (III). This on further oxidation with bromine water gave the corresponding αα′-dimethoxy-β-hydroxy-*l*-araboglutaric acid recognised as its crystalline diamide (IV) (compare Smith, *J.*, 1939, 50). The 4 : 6-dimethyl *d*-galactose derivatives isolated from methylated degraded damson gum as described in the earlier paper must therefore have represented only a small portion of the total dimethyl galactose.

The proof of the identity of the other sugars depends upon the following facts :

(*a*) The 2 : 3 : 5-trimethyl *l*-arabinose was identified after oxidation as the well-characterised crystalline lactone and amide (Humphreys, Pryde, and Waters, *J.*, 1931, 1298).

(*b*) The 2 : 3-dimethyl *l*-arabinose was oxidised to 2 : 3-dimethyl *l*-arabonolactone which was recognised as the corresponding crystalline amide (Smith, *J.*, 1939, 753).

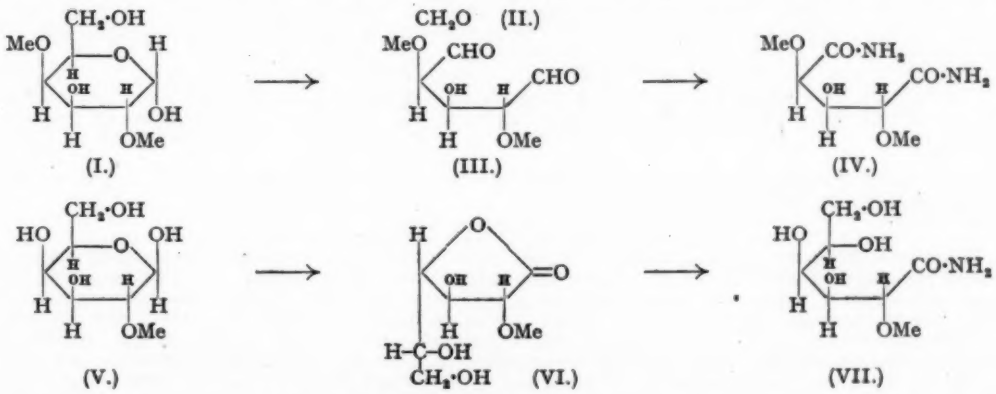
(*c*) Proof of the identity of the trimethyl *d*-galactose depended on the isolation of crystalline 2 : 4 : 6-trimethyl *d*-galactose and its crystalline anilide (Hirst and Jones, *J.*, 1939, 1486).

(*d*) 2-Methyl *d*-galactose (V) was recognised as the crystalline sugar and the corresponding anilide (compare Oldham and Bell, *J. Amer. Chem. Soc.*, 1938, **60**, 323; McCreath and Smith, *J.*, 1939, 390). On oxidation the sugar gave a *γ-lactone* (VI) showing the absence of a methoxyl on C_4. The corresponding *amide* (VII) gave a negative Weerman test showing the presence of a methoxyl group on C_2.

(*e*) 4(?)-*Methyl* d-*galactose* was characterised as the crystalline sugar, and its *anilide*. With phenylhydrazine the sugar gave without loss of methoxyl an *osazone* which appeared to be identical with 4-methyl *d*-galactosazone, while with methyl alcoholic hydrogen chloride the sugar showed no downward change of rotation indicating the presence of a methoxyl on C_4. Since the evidence available is not absolutely conclusive the conclusion that the sugar was 4-methyl *d*-galactose is given with reserve.

(*f*) Proof of the identity of 2 : 3 : 4-trimethyl *d*-glycuronic acid was furnished by its conversion to crystalline 2 : 3 : 4-trimethyl saccharic lactone methyl ester (Charlton, Haworth and Herbert, *J.*, 1931, 2855).

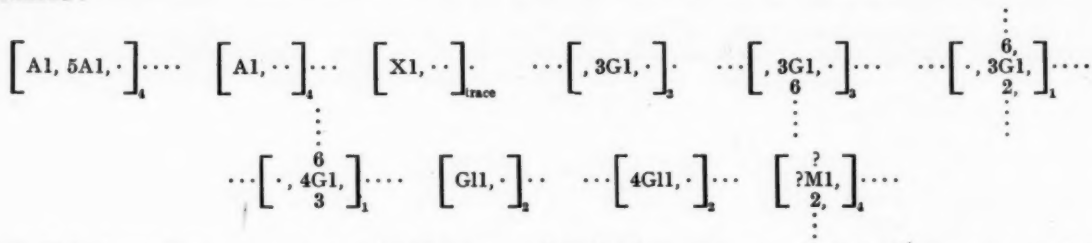
(*g*) The 2 : 3-dimethyl *d*-glycuronic acid was oxidised to 2 : 3-dimethyl *d*-saccharic acid which was identified as crystalline 2 : 3-dimethyl saccharic lactone methyl ester (Hirst and Jones, *J.*, 1939, 1482; Smith, *J.*, 1940, 1043).



The quantitative estimation of the sugars present after hydrolysis was not a simple matter owing to the number of substances involved and their similar properties. In particular it was not found possible to detect small quantities of xylose admixed with arabinose although some was known to be present. In addition, the hydrolysis of the mannose attached to the glycuronic acid molecule appeared to be attended by much decomposition of the mannose fraction and we have, therefore, been unable as yet to isolate the mannose derivative in a pure state. However, from an examination of methoxyl values and refractive indices and from the isolation of crystalline derivatives of the sugars it has been possible to obtain some idea of the relative proportions of the sugars present. The following figures are a provisional estimation of the approximate proportions of sugars formed on the hydrolysis of methylated damson gum : 2 : 3 : 5-trimethyl *l*-arabofuranose (8 parts), 2 : 3-dimethyl *l*-arabinose (4 parts), 2 : 4 : 6-trimethyl *d*-galactose (3 parts), 2 : 4-dimethyl *d*-galactose (3 parts), 2-methyl *d*-galactose (1 part), 4(?)-methyl *d*-galactose (1 part), 2 : 3 : 4-trimethyl *d*-glycuronic acid (2 parts), 2 : 3-dimethyl *d*-glycuronic acid (2 parts), methylated mannose, and methylated xylose. Previous work had shown that the methylated derivative of the " degraded," autohydrolysed, arabinose-free damson gum gave on hydrolysis : 2 : 3 : 4-trimethyl *d*-xylose, 2 : 3 : 4 : 6-tetramethyl *d*-galactose, 2 : 3 : 4-trimethyl *d*-galactose, 2 : 4 : 6-trimethyl *d*-galactose, 2 : 4-dimethyl *d*-galactose, 2 : 3 : 4-trimethyl *d*-glycuronic acid, 2 : 3-dimethyl *d*-glycuronic acid, and an unidentified derivative of *d*-mannose, with a trace of 4 : 6-dimethyl *d*-galactose. It will be observed from a comparison of these two sets of results that the 2 : 3 : 4 : 6-tetramethyl *d*-galactose and 2 : 3 : 4-trimethyl *d*-galactose do not occur among the hydrolysis products of methylated damson gum. It is inferred, therefore, that the arabinose molecules, which are probably all in the furanose form (compare

Hirst and Jones, *loc. cit.*), are attached to the galactose molecules which give rise to 2 : 3 : 4 : 6-tetramethyl *d*-galactose and 2 : 3 : 4-trimethyl *d*-galactose on hydrolysis of the methylated derivative of degraded damson gum. Since only *l*-arabinose is removed during the autohydrolysis of damson gum (Hirst and Jones, *loc. cit.*), and since hydrolysis of the methylated damson gum gave 2 : 3 : 5-trimethyl arabinose and 2 : 3-dimethyl arabinose in the ratio 2 to 1, it follows that there must be two side chains present in each repeating unit composed of arabinose (3 parts), galactose (2 parts), mannose (1 part), and glycuronic acid (1 part), and that these consist of *l*-arabinose only and are united to C_6 and C_3 of the galactose units in the main chain of the molecule. One side chain consists of one molecule of arabofuranose while the other consists of two molecules of *l*-arabofuranose linked to one another through C_1 and C_5, and the reducing group of the resulting disaccharide is united glycosidically to the main chain of the molecule. As the molecular proportions of 2 : 3 : 4-trimethyl and 2 : 3-dimethyl *d*-glycuronic acids appear to be constant in both the methylated degraded and methylated damson gums, it seems that they are not directly combined with any *l*-arabinose molecules. On the other hand, 2- and 4(?)-methyl *d*-galactoses present in the products of hydrolysis of methylated damson gum were not found among the sugars formed on hydrolysis of the methylated degraded gum; it appears, therefore, that the *l*-arabinose molecules are attached in some way to the sugars which give rise to monomethyl *d*-galactose on hydrolysis of the methylated gum. The possibility that the monomethyl *d*-galactoses result from incomplete methylation remains; we prefer to believe, however, that these monomethyl sugars are an integral part of the methylated gum molecule.

It is not possible at this stage to suggest any precise formula for damson gum since many points remain to be determined. For example, whether the polysaccharide is built up of a main chain of galactopyranose units linked alternately through carbon atoms 1, 3 and 1, 6, as seems to be fairly common in the galactose-containing polysaccharides, is as yet unknown. New experimental methods for the determination of the structure of the complex polysaccharides are being developed and by their use it is hoped to solve some of the outstanding problems encountered in this branch of carbohydrate chemistry. It is apparent, however, that the repeating unit of damson gum must be built up of the following residues, the precise order of arrangement being as yet undefined :



where M is *d*-mannopyranose; A is *l*-arabofuranose; G is *d*-galactopyranose; X is *d*-xylopyranose; and Gl is *d*-glycuronic acid.

Experimental.

(a) *Methylation of Damson Gum.*—The purified gum, $[\alpha]_D^{20°}$ − 26°, equiv. wt. 1100 (Hirst and Jones, *J.*, 1938, 1174), (50 g.) was suspended in water (300 c.c.) and brought into solution by the addition of N-thallous hydroxide solution (100 c.c.). An excess of N-thallous hydroxide solution (1½ l.) was evaporated to 300 c.c. in a silver dish and added to the solution of the thallium salt of the gum. The precipitated thallium complex (A) (200 g.) was filtered off, washed with alcohol, and dried. It was a white powder, sparingly soluble in water and containing 76% of thallium titratable with dilute sulphuric acid using phenolphthalein as an indicator. The dry finely powdered thallium complex was boiled in the dark with dry methyl iodide (500 c.c.) for 60 hours. Excess of methyl iodide was removed by distillation and the yellow solid (B) was exhaustively extracted with methyl alcohol. The extract on concentration gave a partially methylated gum, to which was added the filtrate from (A) together with N-thallous hydroxide (330 c.c.), and the mixture was evaporated to dryness at 40°/12 mm. with exclusion of carbon dioxide. The dry solid was finely powdered (120 mesh) and boiled with methyl iodide (300 c.c.). After 60 hours, excess of methyl iodide was removed by distillation and the solid residue exhaustively extracted with methyl alcohol. The alcoholic solution was concentrated to a syrup and dissolved in ethyl alcohol–benzene (200 c.c.). To the solution was added thallous ethoxide [prepared from N-thallous hydroxide (500 c.c.)] and the mixture evaporated to dryness. The powdered solid was boiled with methyl iodide (200 c.c.) as before and the product was isolated in the usual manner. One more treatment with thallous ethoxide, followed by methyl iodide, gave methylated damson gum (41·7 g.). A quantity of incompletely methylated polysaccharide (8·7 g.) was obtained when the solid (B) was extracted with water after the methyl alcoholic extraction.

Methylated damson gum is a white solid, soluble in cold water, benzene, acetone, chloroform, dioxan, *m*-cresol, and methyl alcohol; insoluble in hot water, light petroleum, and ether.

The methylated product (32 g.), OMe 41·5%, was fractionally precipitated from chloroform by means of light petroleum. Four fractions were isolated:

Fraction I. 0·5 g. $[\alpha]_D^{20°}$ − 40° (*c*, 0·57 in methyl alcohol). OMe, 40·3%.
Fraction II. 20·5 g. $[\alpha]_D^{20°}$ − 40° (*c*, 0·65 in methyl alcohol). OMe, 40·5%. $\eta_{sp.}/c$, 0·127 in *m*-cresol.
Fraction III. 5·0 g. $[\alpha]_D^{20°}$ − 39° (*c*, 0·75 in methyl alcohol). OMe, 40·0%. $\eta_{sp.}/c$, 0·108 in *m*-cresol.
Fraction IV. (Residue). 6·0 g. $[\alpha]_D^{20°}$ − 38° (*c*, 0·8 in methyl alcohol). OMe, 41·8%. $\eta_{sp.}/c$, 0·09 in *m*-cresol.

Fraction I contained impurities. Fractions II, III, and IV showed no significant differences and were combined. $[\alpha]_D^{20°}$ − 39° (*c*, 0·6 in methyl alcohol). Equiv. wt., 1410 (by titration with alkali). Uronic anhydride, 13·3% (from the carbon dioxide evolved on heating with 12% hydrochloric acid) (Found : C, 51·5; H, 7·5; OMe, 40·6%).

Partial Hydrolysis of Methylated Damson Gum.—Methylated damson gum (25 g.) was dissolved in 1% methyl alcoholic hydrogen chloride (500 c.c.) and heated under reflux. $[\alpha]_D^{20°}$ − 39° (*c*, 5·0 initial value), − 27° (2/3 hr.), − 12° (2¼ hrs.), − 5° (3¼ hrs.), + 13° (18¼ hrs.), + 13° (21 hrs.); (very little change of rotation on further heating). Hydrochloric acid

was removed with silver carbonate and the solution filtered. On removal of the methyl alcohol a viscid syrup (25·78 g.) was obtained. This was submitted to fractional distillation.

Fraction I. 2 : 3 : 5-Trimethyl methyl-*l*-arabinoside (4·94 g.), b. p. 98°/0·003 mm. (bath temp.), $n_D^{21°}$ 1·4375, OMe, 61·8%, $[\alpha]_D^{20°}$ − 66° (*c*, 0·77 in methyl alcohol).

Fraction II. Dimethyl methyl-*l*-arabinoside admixed with some 2 : 3 : 5-trimethyl methyl-*l*-arabinoside (0·6 g.), b. p. 135°/3·003 mm. (bath temp.), $n_D^{17°}$ 1·4520, OMe, 51·7%, $[\alpha]_D^{20°}$ − 5° (*c*, 0·6 in methyl alcohol).

Complete Hydrolysis of Methylated Damson Gum.—The still residue (20·2 g.), an orange viscid liquid, was dissolved in N-hydrochloric acid (400 c.c.) and heated on the boiling water-bath for 6 hours. (The solution became too dark for polarimetric observation. Some furfural was formed.) The solution was neutralised with silver carbonate, filtered, and the silver salts decomposed with hydrogen sulphide. Silver sulphide was removed by filtration, and the filtrate aerated to remove hydrogen sulphide, neutralised with barium carbonate, and filtered. By this means it was possible to obtain the barium salts of the methylated glycuronic acids, free from admixed barium chloride. The aqueous solution (C) was concentrated at 60°/12 mm. to a small volume (60 c.c.) and exhaustively extracted with benzene in an all-glass apparatus.

The benzene extract on concentration gave a syrup (7·90 g.) which was converted into the glycosides by boiling with 1% methyl alcoholic hydrogen chloride (100 c.c.) for 15 hours. Hydrochloric acid was removed with silver carbonate and the filtered solution concentrated at 760 mm. to a syrup (8·22 g., $n_D^{20°}$ 1·4518) which was fractionally distilled giving :

Fraction III. 2 : 3 : 5-Trimethyl methyl-*l*-arabinoside (3·21 g.), b. p. 100°/0·002 mm., $n_D^{21°}$ 1·4395, $[\alpha]_D^{20°}$ − 31° (*c*, 0·58 in methyl alcohol) (Found : OMe, 58·8. Calc. for $C_9H_{14}O_5$: OMe, 60·8%).

Fraction IV. Mainly dimethyl methyl-*l*-arabinoside (1·81 g.), b. p. 100—130°/0·002 mm., $n_D^{18°}$ 1·4508, $[\alpha]_D^{20°}$ − 7° (*c*, 0·39 in methyl alcohol) (Found : OMe, 49·2. Calc. for $C_8H_{16}O_5$: OMe, 48·4%).

Fraction V. Mainly 2 : 4 : 6-trimethyl methyl-*d*-galactoside (1·77 g.), b. p. 130—160°/0·002 mm., $n_D^{18°}$ 1·4580, $[\alpha]_D^{20°}$ + 36° (*c*, 0·52 in methyl alcohol) (Found : OMe, 50·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

Residue, 1·30 g. (D).

The aqueous solution (C) after extraction was concentrated under reduced pressure to a syrup which was exhaustively extracted with acetone, leaving the barium salts (E) (5·0 g.). Concentration of the acetone extract gave a syrup (8·80 g.) to which was added residue (D) and the whole was converted to the glycosides by boiling with 2% methyl alcoholic hydrogen chloride (100 c.c.) during 15 hours. Hydrochloric acid was removed with silver carbonate and the solution filtered. Concentration of the filtrate at 40°/12 mm. gave a syrup (9·8 g.). This was separated into two fractions by exhaustive extraction with ether : ether soluble (7·62 g.), $n_D^{20°}$ 1·4745; ether insoluble (1·9 g.), $n_D^{19°}$ 1·4830 (F). The ether soluble portion was fractionally distilled in a vacuum.

Fraction VI. 2 : 4 : 6-Trimethyl methyl-*d*-galactoside (1·71 g.), b. p. 126—135°/0·003 mm., $n_D^{19°}$ 1·4595, $[\alpha]_D^{20°}$ + 41° (*c*, 0·80 in methyl alcohol) (Found : OMe, 51·2. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

Fraction VII. 2 : 4-Dimethyl and 2 : 4 : 6-trimethyl methyl-*d*-galactosides (0·89 g.), b. p. 130—150°/0·002 mm., $n_D^{18°}$ 1·4720, $[\alpha]_D^{19°}$ + 55° (*c*, 0·47 in methyl alcohol) (Found : OMe, 45·5%).

Fraction VIII. 2 : 4-Dimethyl methyl-*d*-galactoside (2·85 g.), b. p. 150—160°/0·001 mm. (bath temp.), $n_D^{19°}$ 1·4770, $[\alpha]_D^{17°}$ + 78° (*c*, 0·51 in methyl alcohol) (Found : OMe, 40·9. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

To the still residue (2·19 g.) was added fraction (F) (1·9 g.) and the whole distilled from a flask without a fractionation column.

Fraction IX. 2 : 4-Dimethyl and monomethyl methyl-*d*-galactosides (1·25 g.), b. p. 151—166°/0·002 mm., $n_D^{19°}$ 1·4812, $[\alpha]_D^{19°}$ + 71° (*c*, 0·49 in methyl alcohol) (Found : OMe, 36·8. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction X. Monomethyl methyl-*d*-galactosides (2·15 g.), b. p. 166—210°/0·003 mm., $n_D^{19°}$ 1·4900, $[\alpha]_D^{20°}$ + 63° (*c*, 0·49 in methyl alcohol) (Found : OMe, 29·9. Calc. for $C_8H_{16}O_6$: OMe, 29·8%).

Residue, 0·54 g.

The barium salts (E) (5·0 g.) were dissolved in water and the barium exactly removed as sulphate by the addition of N-sulphuric acid (15·5 c.c.). The solution was spun on the centrifuge to remove barium sulphate, and concentrated under reduced pressure to a syrup which was boiled with 2% methyl alcoholic hydrogen chloride (200 c.c.) for 15 hours. Hydrochloric acid was removed with silver carbonate and the filtered solution concentrated to a syrup (3·27 g.) which was fractionally distilled in a vacuum.

Fraction XI. Methyl ester of 2 : 3 : 4-trimethyl methyl-*d*-glycuronide (0·92 g.), b. p. 140—150°/0·001 mm. (bath temp.), $n_D^{18°}$ 1·4510, $[\alpha]_D^{19°}$ 70° (*c*, 0·59 in methyl alcohol) (Found : Equiv. wt., 273; OMe, 54·0. Calc. for $C_{11}H_{20}O_7$: Equiv. wt., 264; OMe, 58·7%).

Fraction XII. Mainly methyl ester of dimethyl methyl-*d*-glycuronide (0·56 g.), b. p. 150—160°/0·001 mm. (bath temp.), $n_D^{18°}$ 1·4660, $[\alpha]_D^{19°}$ + 64° (*c*, 0·6 in methyl alcohol) (Found : OMe, 48·5. Calc. for $C_{10}H_{18}O_7$: OMe, 49·9%).

Residue, 1·74 g. This was boiled with 5% methyl alcoholic hydrogen chloride (30 c.c.) for 60 hours. Hydrochloric acid was removed with silver carbonate and the filtered solution concentrated at 40°/12 mm. and the residual syrup (1·5 g.) distilled in a vacuum.

Fraction XIII. Methyl ester of trimethyl methyl-*d*-glycuronide admixed with some dimethyl derivative (0·54 g.), b. p. 160—190°/0·001 mm. (bath temp.), $n_D^{23°}$ 1·4670, OMe, 53·0%. (The residue (0·9 g.) was discarded.)

Examination of the Various Fractions.—Fractions I and III (8·15 g.) were combined and a portion (6·29 g.) hydrolysed with N/2-hydrochloric acid (100 c.c.) on the boiling water-bath for 3 hours. $[\alpha]_D^{22°}$ − 50° (*c*, 6·29, initial value in N/2-hydrochloric acid); − 14° (¾ hour); − 11° (1½ hours); − 10° (2¾ hours) (constant value). This equilibrium value would be given by 6·46 g. of trimethyl methyl-*l*-arabofuranoside and 1·69 g. of dimethyl methyl-*l*-arabinoside in fractions I and III combined. Hydrochloric acid was removed with silver carbonate and the solution filtered; silver ions were removed with hydrogen sulphide and the filtered solution concentrated to a syrup under reduced pressure. The syrup (5·70 g.) was freed from a trace of silver sulphide by extraction with acetone, and fractionally distilled in a vacuum.

Fraction XIV. Trimethyl *l*-arabofuranose (4·10 g.), b. p. 120°/0·002 mm. (bath temp.), $n_D^{22°}$ 1·4485, $[\alpha]_D^{21°}$ − 30° (*c*, 4·0 in water) (Found : OMe, 48·6. Calc. for $C_8H_{16}O_5$: OMe, 48·4%).

Fraction XV. Trimethyl *l*-arabofuranose and 2 : 3-dimethyl *l*-arabinose (1·02 g.), b. p. 120—160°/0·002 mm. (bath temp.), $n_D^{21°}$ 1·4615, $[\alpha]_D^{21°}$ + 16·2° (*c*, 1·0 in water) (Found : OMe, 42·0. Calc. for $C_7H_{14}O_5$: OMe, 34·9%).

Residue, 0·28 g. (probably polymerised products). Loss during distillation, 0·32 g.

Oxidation of Fraction XIV.—This fraction (3·98 g.) was dissolved in water (20 c.c.), bromine added (5 c.c.), and the mixture heated on the water-bath at 48° for 4 hours and then at 20° for 15 hours. A further four hours at 40° gave a non-reducing solution. Bromine was removed by aeration and the solution neutralised with silver carbonate and filtered. The filtrate was treated with hydrogen sulphide, the solution filtered from silver sulphide, concentrated to a syrup (3·65 g.; $n_D^{20°}$ 1·4448), and fractionally distilled in a vacuum.

Fraction XVI. 2 : 3 : 5-Trimethyl *l*-arabonolactone (3·02 g.), b. p. 120°/0·002 mm. (bath temp.), $n_D^{20°}$ 1·4445 (supercooled liquid), $[\alpha]_D^{20°}$ − 43·0°, m. p. 30° (Found : OMe, 48·2; equiv. wt., 200. Calc. for $C_8H_{16}O_6$: OMe, 48·9%; equiv. wt., 190).

This fraction had all the constants of an authentic specimen of 2 : 3 : 5-trimethyl *l*-arabonolactone and on treatment with liquid ammonia gave 2 : 3 : 5-trimethyl *l*-arabonamide in quantitative yield. M. p. and mixed m. p. 136°, $[\alpha]_D^{20°}$ + 22° (*c*, 0·73 in ethyl alcohol).

Fraction XVII. 2 : 3 : 5-Trimethyl *l*-arabonolactone admixed with some dimethyl *l*-arabonolactone (0·42 g.), b. p. 120—130°/0·002 mm. (bath temp.), $n_D^{20°}$ 1·4550. This fraction was combined with Fraction XVIII(a) (see below).

Oxidation of Fraction XV.—0·99 G. was dissolved in water (10 c.c.) and bromine added (1·5 c.c.). The oxidation was carried out exactly as described for fraction XIV and gave a syrup (0·89 g.; $n_D^{21°}$ 1·4580) which was fractionally distilled in a vacuum.

Fraction XVIII(a). Dimethyl *l*-arabonolactone admixed with 2 : 3 : 5-trimethyl *l*-arabonolactone (0·42 g.), b. p. 121—138°/0·002 mm. (bath temp.), $n_D^{20°}$ 1·4555. This fraction was combined with Fraction XVII and the constants given below are for the mixture (0·84 g.). Equiv. wt., 182; $[\alpha]_D^{20°}$ − 20·5° (initial value in water, *c*, 0·94); − 19·5° (6½ hours); − 14·4° (70 hours) not constant (Found: OMe, 45·8%). On treatment with liquid ammonia, the lactone gave 2 : 3 : 5-trimethyl *l*-arabonamide, m. p. and mixed m. p. 137°. The residual non-crystalline amide gave a negative Weerman test indicating the absence of any amide with a hydroxyl group on C_3.

Fraction XVIII(b). Dimethyl *l*-arabonolactone (0·20 g.), b. p. 160°/0·002 mm. (bath temp.); $n_D^{20°}$ 1·4638; equiv. wt., 177; $[\alpha]_D^{20°}$ − 22·0° (initial value in water, *c*, 0·59); − 27·2° (5 hours); − 26° (22 hours); − 15·2° (70 hours; not constant) (Found: OMe, 37·5. Calc. for $C_7H_{12}O_5$: OMe, 35·2%). Solution in liquid ammonia, followed by evaporation of the solvent, gave crystals admixed with syrup. Trituration with acetone gave 2 : 3-dimethyl *l*-arabonamide (60 mg.), m. p. and mixed m. p. 160° (after recrystallisation from alcohol).

Fractions II and IV (2·33 g.) were dissolved in hydrochloric acid (100 c.c.) and heated on the boiling water-bath for 2 hours; $[\alpha]_D^{21°}$ − 5° (*c*, 2·33, initial value in N-hydrochloric acid); + 46° (2 hours, constant value). Hydrochloric acid was removed with silver carbonate and the filtered solution treated with hydrogen sulphide to remove any dissolved silver salts, and concentrated to a syrup (1·90 g.), $n_D^{20°}$ 1·4710, $[\alpha]_D^{20°}$ + 52° (*c*, 1·1 in water) (Found: OMe, 35·4%. Calc. for $C_7H_{14}O_5$: OMe, 34·9%). From the rotation of the free sugar (+ 52°) it can be calculated that this fraction contains 0·87 g. of trimethyl methyl-*l*-arabofuranoside and 1·50 g. dimethyl methyl-*l*-arabinoside.

The syrup (1·85 g.) was dissolved in water (10 c.c.) and bromine (3 c.c.) added. The oxidation product was worked up exactly as described for Fraction XIV, and gave a syrup (1·65 g.) which was fractionally distilled in a vacuum.

Fraction XIX. 2 : 3 : 5-Trimethyl *l*-arabonolactone (0·33 g.), b. p. 110°/0·001 mm. (bath temp.), $n_D^{19°}$ 1·4472, m. p. 27°, $[\alpha]_D^{21°}$ − 40° (*c*, 1·0, initial value in water) (Found: OMe, 48·4; equiv. wt., 198. Calc. for $C_8H_{14}O_5$: OMe, 48·9%; equiv. wt., 190). On treatment with liquid ammonia it gave the corresponding amide in quantitative yield, m. p. and mixed m. p. 137°; $[\alpha]_D^{20°}$ + 23° (*c*, 0·7 in ethyl alcohol).

Fraction XX. 2 : 3-Dimethyl *l*-arabonolactone (1·25 g.), b. p. 140—150°/0·001 mm. (bath temp.), $n_D^{25°}$ 1·4600 (Found: OMe, 38·3; equiv. wt., 188. Calc. for $C_7H_{12}O_5$: OMe, 35·2%; equiv. wt., 176), $[\alpha]_D^{21°}$ + 4° (*c*, 1·4, initial value in water); − 2° (1 hour); − 8° (5 hours); − 11° (7 hours); − 10° (24 hours); − 10° (74 hours). These rotation figures are in agreement with a mixture of 70% 2 : 3-dimethyl *l*-arabonolactone and 30% 2 : 4 : 6-trimethyl *d*-galactonolactone, or with a mixture of 2 : 3-dimethyl *l*-arabonolactone and some other dextro-rotatory dimethyl pentono-lactone.

Still residue. 0·20 G.; not further examined.

The lactone (1·20 g.) (Fraction XX) on treatment with liquid ammonia gave crystalline 2 : 3-dimethyl *l*-arabonamide, m. p. and mixed m. p. 159°, $[\alpha]_D^{21°}$ + 17° (*c*, 0·52 in water) (Found: OMe, 33·1. Calc. for $C_7H_{15}O_5N$: OMe, 32·1%). The residual amide (0·45 g.) could not be induced to crystallise. With sodium hypochlorite it gave sodium cyanate isolated as hydrazodicarbonamide. The yield indicated the presence of some 0·15 g. of an amide with a hydroxyl on C_3. From the above figures it is estimated from rotational data and from refractive index values that the total amount of 2 : 3-dimethyl *l*-arabinose present in fractions I, II, III, and IV was 2·81 g.

Fraction.	Weight (g.) as glucosides.	2 : 3 : 5-Trimethyl methyl -arabinoside.	2 : 3-Dimethyl methyl -arabinoside.	2 : 4 : 6-Trimethyl methyl	2 : 4-Dimethyl methyl -*d*-galactosides.	2-Methyl methyl	4(?)-Methyl methyl	2 : 3 : 4-Trimethyl methyl -glycuronosides.	2 : 3-Dimethyl methyl -glycuronosides.
I	4·94	6·46 [1]	1·69 [1]	—	—	—	—	—	—
III	3·21								
II	0·60	0·87 [2]	1·50 [2]	—	—	—	—	—	—
IV	1·81								
V	1·77	—	—	1·71 [3]	—	—	—	—	—
VI	1·71	—	—	1·44 [3]	—	—	—	—	—
VII	0·89	—	—	0·20	0·69 [3]	—	—	—	—
VIII	2·85	—	—	—	2·34 [3]	—	—	—	—
IX	1·25	—	—	—	0·92 [3]	0·16	0·16	—	—
X	2·15	—	—	—	0·10	1·0	1·0	—	—
XI	0·92	—	—	—	—	—	—	0·62	0·30
XII	0·56	—	—	—	—	—	—	0·46	0·64
XIII	0·53								
	23·20	7·33	3·19	3·35	4·05	1·16	1·16	1·08	0·94
Calculated yields of glycosides from 25 g. of polysaccharide:		7·86	3·67	2·36	4·23	1·19	1·99	2·50	2·38

[1] Fractions I and III combined. [2] Fractions II and IV combined. [3] From yield of anilide: for method of calculation see Part II.

Fraction V (1·77 g.). This fraction partially crystallised on distillation. The mixture of syrup and crystals was tiled; the syrup was absorbed, leaving crude 2 : 4 : 6-trimethyl β-methyl-*d*-galactoside (0·41 g.), m. p. 102°, $[\alpha]_D^{21°}$ + 18° (*c*, 0·34 in methyl alcohol) after recrystallisation from ether–light petroleum. When left in air the galactoside absorbed water giving the *hemihydrate*, m. p. 83—85° (Found: C, 48·9; H, 9·0; OMe, 50·7. $C_{10}H_{20}O_6,\frac{1}{2}H_2O$ requires C, 48·9; H, 8·6; OMe, 50·6%).

The glycoside (0·34 g.) was hydrolysed with N-hydrochloric acid (25 c.c.) on the boiling water-bath for 2¼ hours, $[\alpha]_D^{21°}$ + 72° (*c*, 1·38; equilibrium value). Hydrochloric acid was removed with silver carbonate and the filtered solution concentrated to a syrup which was dissolved in ether and filtered. Concentration of the syrup gave crystalline 2 : 4 : 6-trimethyl α-*d*-galactose, m. p. alone or on admixture with an authentic specimen, 105°, after recrystallisation from ether; $[\alpha]_D^{21°}$ + 122°, falling to + 86° in 24 hours (*c*, 1·2 in water) (Found: OMe, 42·3. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

The sugar (0·1 g.), on heating with aniline (0·2 c.c.) in ethyl alcohol (5 c.c.) during 5 hours and subsequent removal of the alcohol by distillation, gave 2 : 4 : 6-trimethyl *d*-galactose anilide, m. p. 179° (after recrystallisation from absolute

alcohol) (Found: C, 60·5; H, 7·35; N, 5·0. Calc. for $C_{15}H_{29}O_5N$: C, 60·5; H, 7·8; N, 4·7). The m. p. was not depressed by an authentic specimen prepared by Dr. E. G. V. Percival in the Edinburgh laboratories, but was depressed to 156° on admixture with a specimen of 2 : 3 : 4-trimethyl *d*-galactose anilide, m. p. 170°.

The sugar (0·2 g.) was dissolved in water (5 c.c.) and oxidised with bromine (1 c.c.) in the manner described above. The lactone (0·15 g.) was isolated as a syrup which was distilled in a vacuum, b. p. 160°/0·001 mm. (bath temp.); $n_D^{17°}$ 1·4700, $[\alpha]_D^{21°}$ + 143° (initial value in water, *c*, 0·46); + 117° (¾ hour); + 95° (2½ hours); + 69° (4½ hours); + 61° (8½ hours); + 52° (11 hours, constant value) (Found: equiv. wt., 222; OMe, 41·2. Calc. for $C_9H_{16}O_6$: equiv. wt., 220; OMe, 42·4%). The lactone on treatment with methyl alcoholic ammonia gave the crystalline amide in quantitative yield, m. p. 166° (after recrystallisation from acetone), $[\alpha]_D^{20°}$ + 73° (*c*, 0·72 in water). Treatment of the amide with sodium hypochlorite under the conditions described by Weerman gave no sodium cyanate showing the presence of the methoxyl group in position 2.

The syrup absorbed by the tile (1·36 g.) was extracted with ether and a portion of it (0·71 g.) was dissolved in N-hydrochloric acid (30 c.c.) and heated on the boiling water during 2½ hours; $[\alpha]_D^{21°}$ + 36° (*c*, 2·4, initial value); + 54° (1 hour); + 56° (2½ hours, constant value). Hydrochloric acid was removed by neutralising with silver carbonate and the solution filtered. Silver salts were removed from solution as silver sulphide and the solution concentrated to a syrup which was exhaustively extracted with acetone. The extracts on concentration gave a syrup (0·65 g.), $n_D^{22°}$ 1·4665; $[\alpha]_D^{20°}$ + 60° (*c*, 1·0 in water). In order to estimate the amount of 2 : 4 : 6-trimethyl *d*-galactose, the syrup (0·65 g.) was heated under reflux for 2 hours with alcohol (10 c.c.) containing aniline (1 c.c.). On removal of the alcohol by distillation the syrup crystallised. The anilide was triturated with alcohol–ether and filtered. Yield of anilide 0·40 g., m. p. 179°. The filtrate on concentration gave a further crop of crystals (0·20 g.). The total yield of anilide was thus 0·60 g. from 0·65 g. of sugar. The total yield of 2 : 4 : 6-trimethyl methyl-*d*-galactoside in this fraction was 1·71 g. No trace of 2 : 3 : 4-trimethyl *d*-galactose anilide could be detected. A mannose derivative may have been present in this fraction as the free sugar had a low rotation.

Fraction VI (1·71 g.). This fraction (1·45 g.) was dissolved in N-hydrochloric acid (40 c.c.) and heated on the boiling water-bath during 2½ hours; $[\alpha]_D^{20°}$ + 53° (*c*, 3·6, initial value in N-hydrochloric acid); + 76° (½ hour); + 70° (1½ hours); + 69° (2½ hours, constant value). The solution was neutralised with silver carbonate, filtered and the filtrate evaporated to a syrup (1·35 g.). $[\alpha]_D^{20°}$ + 73° (in water, *c*, 1·2). It did not crystallise on nucleation with 2 : 4 : 6-trimethyl *d*-galactose. The syrup was dissolved in alcohol (15 c.c.) containing aniline (2 c.c.) and heated under reflux during 2 hours. Alcohol was removed by distillation and the residual syrup nucleated with 2 : 4 : 6-trimethyl *d*-galactose anilide, when it crystallised. The crystals (0·90 g.) were triturated with ether and filtered. Concentration of the mother liquors gave a further crop of crystals (0·20 g.). Total yield (1·10 g.), m. p. 179° after recrystallisation from absolute alcohol. This corresponds to 1·44 g. of 2 : 4 : 6-trimethyl methyl-*d*-galactoside in this fraction; no other sugar could be detected.

Fraction VII (0·80 g.) was dissolved in N-hydrochloric acid (30 c.c.) and the solution heated on the boiling water-bath for 5½ hours. $[\alpha]_D^{22°}$ + 70° (initial value); + 73° (1½ hours); + 71° (3 hours); + 71° (5½ hours, constant value). Hydrochloric acid was removed by addition of silver carbonate and the filtered solution concentrated to a syrup (0·75 g.), $[\alpha]_D^{22°}$ + 76° (*c*, 2·0 in water), which did not crystallise. The syrup (0·70 g.) was dissolved in alcohol (10 c.c.) containing aniline (1 c.c.) and boiled for 2 hours. On removal of the solvent by distillation the residual syrup crystallised. The crystals (0·40 g.) were isolated after trituration with ether. M. p. and mixed m. p. with 2 : 4-dimethyl *d*-galactose anilide 207°. This corresponds to 0·69 g. of 2 : 4-dimethyl methyl-*d*-galactoside (calculated on the basis of a 50% yield of anilide; Hirst and Jones, *J.*, 1939, 1488).

Fraction VIII (2·85 g.) slowly crystallised. Crystal growth was accelerated by placing the syrup in an incubator at 50°. The syrup was triturated with acetone–ether and the resulting crystals of 2 : 4-dimethyl β-methylgalactoside (0·60 g.) were filtered off and washed with acetone–ether. M. p. 162°. $[\alpha]_D^{20°}$ + 5° (*c*, 1·0 in methyl alcohol) after recrystallisation from acetone (Found: C, 48·8; H, 8·1; OMe, 42·0. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2; OMe, 41·9%).

The crystals (0·5 g.) were dissolved in N-sulphuric acid (50 c.c.) and heated on the boiling water-bath for 5 hours. $[\alpha]_D^{20°}$ + 72·0° (equilibrium value). Sulphuric acid was removed with barium carbonate and the neutral solution filtered and concentrated under reduced pressure. The residual syrup was exhaustively extracted with acetone, and the extracts concentrated under reduced pressure to a syrup (0·45 g.) which crystallised on exposure to moist air. The crystals were triturated with ethyl acetate and filtered, giving the α-form of the monohydrate of 2 : 4-dimethyl *d*-galactose (0·4 g.), m. p. 105° and mixed m. p. 105° (after recrystallisation from ethyl acetate). The filtrate from crystalline 2 : 4-dimethyl β-methyl-*d*-galactoside was concentrated to a syrup (2·2 g.) which was hydrolysed with N-hydrochloric acid (50 c.c.) during 5 hours. $[\alpha]_D^{19°}$ + 89° (initial value); + 81° (2½ hours); + 76° (3½ hours, constant value). Hydrochloric acid was removed with silver carbonate and the solution filtered and worked up in the usual way to give a syrup (1·8 g.) which crystallised on nucleation with 2 : 4-dimethyl *d*-galactose monohydrate. The syrupy mass was triturated with acetone and filtered. The crystals (0·90 g.) had m. p. and mixed m. p. with an authentic specimen of 2 : 4-dimethyl *d*-galactose monohydrate, 105°. The non-crystalline residue was refluxed with alcoholic aniline giving crystalline 2 : 4-dimethyl *d*-galactose anilide (0·50 g.), m. p. and mixed m. p. 207°. These figures show the presence of 2·34 g. of 2 : 4-dimethyl methyl-*d*-galactoside in this fraction.

Identification of 2 : 4-*Dimethyl* d-*Galactose*.—The sugar (0·50 g.) was dissolved in water (15 c.c.) and periodic acid (1·00 g., excess) added. The rotation of the solution fell from + 84° to + 58° in 40 minutes, and the solution became orange in colour. After 12 hours, the solution was neutralised with barium carbonate and filtered. The filtrate reduced Fehling's solution and contained formaldehyde, recognised by its odour. Evaporation of the filtrate gave a syrup (0·35 g.) which was oxidised with bromine water in the presence of barium carbonate. The solution became non-reducing to Fehling's solution in two hours. Bromine was removed by aeration and the filtered solution evaporated to a syrup and esterified for 8 hours with 2% methyl alcoholic hydrogen chloride. Hydrochloric acid was removed with silver carbonate, the filtered solution evaporated to dryness, and the residue exhaustively extracted with chloroform. Concentration of the extracts gave the dimethyl ester of αα′-dimethoxy β-hydroxy *l*-araboglutaric acid (0·20 g.; $n_D^{19°}$ 1·4495; $[\alpha]_D^{20°}$ + 48° (*c*, 4·0 in methyl alcohol)) which was distilled in a vacuum, b. p. 135°/0·001 mm. (bath temp.), $n_D^{17°}$ 1·4470, $[\alpha]_D^{20°}$ + 50° (*c*, 2·17 in methyl alcohol) (Found: equiv. wt., 123; OMe, 51. Calc. for $C_7H_{14}O_7$: equiv. wt., 118; OMe, 53·3%). The ester with methyl alcoholic ammonia gave the corresponding di-amide in good yield, $[\alpha]_D^{20°}$ + 60° (in water), m. p. 284° (decomp.) after recrystallisation from water–acetone, not depressed on admixture with an authentic specimen supplied by Dr. F. Smith of Birmingham University (Found: N, 13·2. Calc. for $C_7H_{14}O_5N_2$: N, 13·6%).

Fraction IX (1·21 g.), was partially crystalline and was triturated with acetone–ether and filtered. The crystals (0·15 g.) were washed with ether and dried, m. p. 106—110°. These crystals were a mixture of the α- and β-form of 2 : 4-dimethyl methyl-*d*-galactoside, since on hydrolysis with N-hydrochloric acid they gave the monohydrate of 2 : 4-dimethyl *d*-galactose, m. p. and mixed m. p. 105°. The filtrate was concentrated to a syrup (1·06 g.) and hydrolysed with N-hydrochloric acid (50 c.c.). $[\alpha]_D^{19°}$ + 93° (*c*, 2·12, initial value); + 74° (1 hour); + 66° (2 hours, constant value). The solution was neutralised with silver carbonate, filtered and concentrated under reduced pressure to a syrup (0·95 g.). This syrup did not crystallise on nucleation with 2 : 4-dimethyl *d*-galactose monohydrate. It was dissolved in absolute

alcohol (10 c.c.) containing aniline (0·45 c.c.) and heated under reflux for 2 hours. On cooling, 2 : 4-dimethyl *d*-galactose anilide (0·47 g.) separated and was filtered off and washed with alcohol and ether. M. p. and mixed m. p. 207° (decomp.). The filtrate on concentration gave a syrup which crystallised on the addition of a little ether. After standing, the crystals were triturated with alcohol containing ether and filtered off (0·15 g.). The crystals had m. p. 150°, raised to 165° on recrystallisation from alcohol–ether, mixed m. p. with 2-methyl *d*-galactose anilide, 165°. The mother liquors on standing gave a further crop (0·10 g.) of crystals, m. p. and mixed m. p. with 2-methyl *d*-galactose anilide, 165° (see below). The residual syrupy anilides were dark brown, and no crystalline material could be isolated from them. The syrupy anilides were decomposed with hot N-hydrochloric acid (20 c.c.) for 2 hours. Hydrochloric acid was removed as silver chloride and aniline extracted with benzene. The aqueous solution was concentrated to a syrup at 50°/0·12 mm. and the sugars converted to the glycosides (0·20 g.) by refluxing with 2% methyl alcoholic hydrogen chloride (20 c.c.), but, since no crystalline material could be isolated, they were not further investigated.

Fraction X. 2- and 4(?)-Monomethyl *d*-galactose (2·15 g.). This fraction (1·90 g.) was dissolved in N-hydrochloric acid (50 c.c.) and heated on the boiling water-bath for 3 hours, $[\alpha]_D^{21°}$ + 72° (initial value); 80° (1 hour); 76° (3½ hours, constant value). The solution was worked up as described above. Concentration of the neutral aqueous solution gave a syrup (1·75 g.) which rapidly crystallised. Trituration with acetone–methyl alcohol gave crystals (1·1 g.), m. p. 156—180°. Recrystallisation from methyl alcohol and then from glacial acetic acid gave two compounds in approximately equimolecular proportions. A more soluble crystalline fraction was identified as β-2-methyl *d*-galactose, m. p. 147°. $[\alpha]_D^{21°}$ + 49° (*c*, 0·72 in water); + 59° (½ hour); + 65° (1 hour); + 70° (1 hour); + 76·0° (2½ hours); + 80° (6 hours, constant value) (Found: C, 43·4; H, 7·39; OMe, 16·5. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·22; OMe, 16·0%). When heated with alcoholic aniline the sugar gave an anilide, m. p. 165°, not depressed on admixture with a sample of 2-methyl *d*-galactose anilide previously prepared by Dr. F. Smith of Birmingham University (Found: C, 57·6; H, 7·09; N, 5·0; OMe, 9·8. Calc. for $C_{13}H_{19}O_5N$: C, 57·8; H, 7·13; N, 5·2; OMe, 11·5%). On heating with phenylhydrazine in alcohol it gave 2-d-*galactosephenylhydrazone*, m. p. 140—141° (Found: C, 54·8; H, 7·2; N, 9·45. $C_{13}H_{20}O_5N_2$ requires C, 54·8; H, 7·1; N, 9·85%).

The sugar (0·20 g.) on oxidation with bromine in the usual manner gave the syrupy *lactone* of the corresponding acid (0·18 g.), $[\alpha]_D^{20°}$ − 27° (*c*, 1·5 in water) mutarorating very slowly to − 24° (100 hours, value still rising) (Found: equiv. wt., 192; OMe, 16·5. $C_7H_{12}O_6$ requires equiv. wt., 192; OMe, 16·1%).

The lactone on solution in liquid ammonia gave in a syrupy form 2-*methyl galactonamide*, $[\alpha]_D^{22°}$ + 27·0° (*c*, 4·9 in water) (Found: OMe, 14·5. $C_7H_{15}O_6N$ requires OMe, 14·9%). This amide on treatment with sodium hypochlorite under the conditions described by Weerman (*loc. cit.*) gave a negative test showing the presence of a methoxyl group in C_2.

The more insoluble crystalline sugar was β-4(?)-*methyl* d-*galactose*, m. p. 207°, $[\alpha]_D^{20°}$ + 62° (*c*, 1·5 in water), rising to + 92° (in 9 hours) (Found: C, 42·9; H, 7·10; OMe, 16·5. $C_7H_{14}O_6$ requires C, 43·2; H, 7·22; OMe, 16·0%). In cold 1% methyl alcoholic hydrogen chloride, the crystals had $[\alpha]_D^{21°}$ + 126° (*c*, 3·0 — constant value). On heating with alcoholic aniline, the sugar gave 4(?)-*methyl galactose anilide*, m. p. 168° (Found: C, 57·6; H, 7·2; N, 5·36. $C_{13}H_{19}O_5N$ requires C, 57·8; H, 7·13; N, 5·2%). With excess of phenylhydrazine acetate at 70° the sugar gave the *osazone*, m. p. 150° (decomp.) (quoted with reserve since only a small amount of material was available) (Found: OMe, 8·3. $C_{19}H_{24}N_4O_4$ requires OMe, 8·3%.)

The non-crystalline sugars (0·60 g.) on oxidation gave a lactone (0·60 g.), OMe, 17·6%. Equiv. wt. 194. $[\alpha]_D^{20°}$ + 18°, falling to + 9° in 12 hours (*c*, 1·08 in water). Solution in liquid ammonia gave the mixed amides from which 2 : 4-dimethyl *d*-galactonamide (0·10 g.) separated. M. p. and mixed m. p. with an authentic specimen, 164° (after previous sintering at 100°). The residual non-crystalline amide gave a positive Weerman test.

Uronic Acid Fractions.—Fraction XI. A portion (0·56 g.) was hydrolysed with N-hydrochloric acid (25 c.c.) at 90—95° for 12 hours. Owing to opalescence of the solution, change of rotation was not observable. Hydrochloric acid was removed with silver carbonate and hydrogen sulphide bubbled through the filtered solution to remove silver as sulphide and the solution again filtered. Concentration of the filtrate at 40°/12 mm. gave a syrup (0·47 g.), $n_D^{19°}$ 1·4750. OMe, 38·9%. Equiv. wt., 236. $[\alpha]_D^{20°}$ + 54° (in water, *c*, 1·4). The syrup was oxidised with bromine water at 60° for 10 hours. The solution was worked up in the usual way and the residual syrup esterified with methyl alcoholic hydrogen chloride, neutralised with silver carbonate, the methyl alcohol boiled off, and the syrupy residue distilled in a vacuum, b. p. 140°/0·002 mm. (bath temp.), $n_D^{18°}$ 1·4600. The distillate crystallised to a solid mass of methyl 2 : 3 : 4-trimethyl *d*-saccharolactone, m. p. and mixed m. p. 110° (after recrystallisation from ether). $[\alpha]_D^{20°}$ + 100° (*c*, 0·6 in alcohol).

Fractions XII and XIII (1·10 g.) were combined and hydrolysed with N-hydrochloric acid (30 c.c.) at 90—95° during 5 hours. $[\alpha]_D^{20°}$ changed from + 72° to + 30° (constant value). The solution was worked up as for Fraction XI (above), giving a syrup (0·78 g.), $n_D^{18°}$ 1·4880, $[\alpha]_D^{20°}$ + 36° (in water, *c*, 1·7) (Found: equiv. wt., 224; OMe, 32·6. Calc. for 2 : 3-dimethyl *d*-glycuronic acid, $C_8H_{14}O_7$: equiv. wt., 224; OMe, 27·7%).

The sugar acid (0·70 g.) was oxidised with bromine water and worked up as above and the dimethyl saccharic acid esterified and distilled in a vacuum, b. p. 140—170°/0·002 mm., $n_D^{18°}$ 1·4700. The distillate crystallised on standing and by trituration with warm ether the crystals were separated into ether-soluble 2 : 3 : 4-trimethyl methyl-*d*-saccharolactone, m. p. and mixed m. p. 110°, and ether-insoluble 2 : 3-dimethyl methyl-*d*-saccharolactone, m. p. and mixed m. p. with an authentic specimen 101°, depressed to 81° on admixture with 2 : 3 : 4-trimethyl methylsaccharolactone (Found: C, 46·2; H, 6·1; OMe, 38·3. Calc. for $C_9H_{14}O_7$: C, 46·2; H, 6·0; OMe, 39·7%).

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101. *The Application of the Method of Molecular Rotation Differences to Steroids. Part II. Unsaturated Sterols and their Derivatives.*

By D. H. R. BARTON.

The data available in the literature on the optical rotatory powers of unsaturated sterols and their derivatives have been correlated by critical examination of their molecular rotation differences (M.R.D.'s). It is shown that the M.R.D's (Δ values) between unsaturated sterols and their fully hydrogenated analogues are characteristic of the position and type of unsaturation in any part of the molecule. A number of sterols previously considered to be impure (Part I; Barton, *J.*, 1945, 813) also show anomalies when examined by the

procedure developed in this paper: in general the conclusions reached in Part I are confirmed, wherever this is possible, by the data discussed here.

Revised or new formulations are proposed for ergosterols B_1, B_2, and D, and dihydroergosterol II is suggested to be identical with α-dihydroergosterol. Critical examination of both the physical and chemical evidence concerning β-dihydrofucosterol, dihydroergosterol III, ergosterols E and F, β-ergostadiene, and the $\Delta^{6,8(14)}$- and $\Delta^{7,9}$-cholestadienes shows that these substances are not homogeneous.

The development of a further rule correlating the optical rotatory powers of dienes and αβ-unsaturated ketones in the steroid series is described.

THE chemistry peculiar to the steroid group as a whole dictates two general methods of approach in effecting correlation between optical rotatory power and structure. The first, which has already been developed in Part I (Barton, *loc. cit.*), deals with the changes in optical rotatory power produced by transformations at the 3 position, and is particularly useful in characterising and differentiating naturally occurring sterols and triterpenoids (compare Barton and Jones, *J.*, 1944, 659). The second method, which is valuable in dealing with the more detailed chemistry of the group and in characterising conjugated dienes and substances of high rotatory power, is developed in this communication. It depends upon the differences in molecular rotation observed when unsaturated compounds are compared with their corresponding saturated analogues (in this paper with rings A and B in the *trans* position). The relationship need only be a formal one and it is not necessary that these transformations be effected by direct chemical methods.

The procedure is conveniently illustrated by the data listed in Table I. The term " Δ value," which is used throughout this paper, signifies the difference observed when the molecular rotation of the unsaturated substance is subtracted from the molecular rotation of its saturated analogue. Thus the Δ value of cholesterol is the molecular rotation of cholestanol less that for cholesterol itself, while for ketones, like Δ^4-cholestenone, it is defined as the value for cholestane less that for the ketone. Where the molecular rotation of a substance has been quoted before, it is not repeated here and the Δ values in Table I can easily be checked by reference to Part I. It will be noted that the Δ value for any sterol is highly characteristic of the type of nuclear unsaturation in that compound and that it varies to some extent as the C_3 hydroxyl is acylated. These facts permit a facile evaluation of double bond position. There are, therefore, three general methods of characterising the nuclear unsaturation in a sterol: the M.R.D.'s (Δ values) on acylation and on reduction, which are reasonably precise, and the absolute magnitudes of the rotatory powers, which are good working guides.

TABLE I.

Substance type.	Position of nuclear double bond (⌐¬).	Sterols. No. of examples.	Sterols. A.M.* of Δ values.	Sterols. Limits of variation from A.M.	Acetates. No. of examples.	Acetates. A.M. of Δ values.	Acetates. Limits of variation from A.M.	Benzoates.† No. of examples.	Benzoates.† A.M. of Δ values.	Benzoates.† Limits of variation from A.M.	Refs.
Δ^5-Stenols	5 : 6	6	+251‡	+10 to −9	6	+243	+27 to −18	6	+173	+16 to −27	1
γ-Stenols	7 : 8	2	+ 77	+16 to −17	2	+ 57	+3 to −4	1	+ 64	—	1
δ-Stenols	8 : 9	1	+ 48	—	1	± 0	—	—	—	—	1
α-Stenols	8 : 14	4	+ 9	+7 to −8	4	+ 14	+9 to −9	2	+ 53	+6 to −6	1
ε-Stenols	9 : 11	1	−100	—	1	− 77	—	1	−103	—	1
β-Stenols	14 : 15	3	− 24	+12 to −7	3	− 20	+16 to −14	1	− 59	—	1
7-Dehydro-Δ^5-stenols	5 : 6 and 7 : 8	5	+538	+40 to −40	3	+384	+21 to −27	2	+370	+13 to −13	1

* Arithmetic mean.

† Dinitrobenzoates are included under this heading as their molecular rotations are almost identical with those of the corresponding benzoates (see Reference 1).

‡ All rotations in this paper are in $CHCl_3$ for the Na_D line unless specified to the contrary.

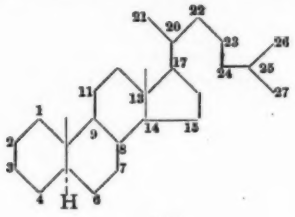
Table II lists a number of sterols whose Δ values are anomalous. The purity or assigned structures of bombicesterol, spongillasterol and Heilbron's Sterol B have already been questioned in Part I, and it is consequently not surprising that they show this anomalous behaviour when re-examined by the method developed here. Fucosterol is considered to be $\Delta^{5,24(28)}$-stigmastadienol (MacPhilllamy, *J. Amer. Chem. Soc.*, 1942, **64**, 1732) and its dihydro-derivatives can now be characterised. In agreement with Coffey, Heilbron, and Spring (*J.*, 1936, 738) α-dihydrofucosterol clearly possesses a 5 : 6-double bond and is thus identical with β-sitosterol. On the other hand β-dihydrofucosterol also appears to be substantially a 5 : 6 stenol; since both isomers are said to yield stigmastanol on complete hydrogenation (Heilbron *et al.*, *J.*, 1935, 1205), it is

TABLE II.

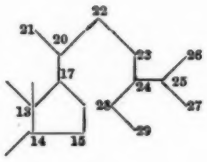
Substance.	Suggested position of ⌐¬: literature.	Suggested position of ⌐¬: this paper.	$[M]_D$ Sterol etc. Sterol.	$[M]_D$ Sterol etc. Acetate.	$[M]_D$ Stanol etc. Stanol.	$[M]_D$ Stanol etc. Acetate.	Δ values. Sterol.	Δ values. Acetate.	Refs.
Bombicesterol	—	Impure	−124	−188	− 43	+ 43	+ 81	+231	1
α-Dihydrofucosterol	5 : 6	5 : 6	−157	−201	+100	+ 69	+257	+270	1, 2
β-Dihydrofucosterol	—	Mixture	−124	−178	+100	+ 69	+224	+247	1, 2
Spongillasterol	22 : 23	5 : 6 with some impurity	−174	−219	+100	+ 69	+274	+288	1
Sterol B	24 : 28	Mixture	−107	−128	+ 25	− 37	+132	+ 91	1

likely that the β-compound is a mixture of the α-derivative with some stigmastanol. This conclusion is supported by the anomalous optical behaviour of *epi*-β-dihydrofucosterol (compare Callow and Strain, *Proc. Roy. Soc.*, **1936**, A, **157**, 194), which can be interpreted on similar grounds.

In the same way as with nuclear unsaturation, the positions of double bonds in the side chains of sterols can be readily characterised. Table III lists sterols which may be compared in this way. Reduction of the $C_{22:23}$ bond is accompanied by an increase of approximately 61 in molecular rotation. There is one exception, ergosterol peroxide, to this generalisation and the most reasonable explanation of the discrepancy is that the rotation of this substance has been incorrectly recorded.



(I.)
Cholestane series.



(II.)
Stigmastane series.

TABLE III.

Substance.	Position of formally reduced ⊨.	Δ values. Sterols.	Acetates.	Dinitrobenzoates.*	A.M. of all values.	Limits of variation from A.M.	Refs.
Brassicasterol	22 : 23	+ 62	+ 89	+68			1
Ergosterol	22 : 23	+ 81	+ 42	—			1
$\Delta^{6,22}$-Ergostadien-3(β) : 5 : 6-triol	22 : 23	+ 60	—	—	+61	+28 to −19	3, 4, 5
Poriferasterol	22 : 23	+ 53	+ 49	+48			1
Stigmasterol	22 : 23	+ 49	+ 63	+72			1
24 : 25-Dehydrocholesterol	24 : 25	− 5	—	− 1			1, 6
Zymosterol	24 : 25	+ 1	− 8	+11	+ 1	+10 to −8	1, 6
epi-Zymosterol	24 : 25	+ 5	—	—			1, 6
Fucosterol	24 : 28	+ 20	+ 26	+10	+19	+7 to −9	1
Anomalous.							
Ergosterol peroxide	22 : 23	+176 †	+132	—	—	—	5, 7

* Includes benzoates.

† The rotation of 7-dehydrocholesterol peroxide (Reference 18) is in good agreement with that for the dihydroergosterol peroxide and no doubt it is the specific rotation of ergosterol peroxide itself which is erroneous.

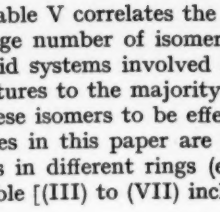
When a sterol contains two double bonds, one in the side chain and one in the nucleus, each makes a separate contribution to the Δ value observed on complete hydrogenation. Thus if the position of one double bond is known, it is a simple matter to deduce that of the second. Table IV illustrates this procedure. The Δ values for the nulcear ethenoid linkages in α-dihydroergosterol and α-spinasterol are in good agreement with the Δ^7 formulations (Barton, *loc. cit.*), but not with the values for Δ^8 or $\Delta^{8(14)}$ unsaturation, which double bond positions have formerly been proposed. Assuming the Δ^7 positions of the nuclear double bonds suggested in Part I for β- and δ-spinasterols, it is to be anticipated that a $C_{22:23}$ linkage is absent in these sterols, and that the side chain unsaturation is $C_{24:25}$ and $C_{25:26}$. It will be of interest to see whether these predictions will be verified, and whether the tentative suggestion of Ruigh (*Ann. Rev. Biochem.*, **1945**, **14**, 225) that the spinasterols differ from each other in position of the nuclear unsaturation will be proved incorrect. The Δ values for the minor yeast sterols, assuming the positions of nuclear unsaturation detailed in Part I, are not incompatible with the side chain formulations suggested in the literature (Wieland, Rath, and Hesse, *Annalen*, 1941, **548**, 34). The optical rotatory power data for dihydroergosterols II and III are specially interesting. The Δ values for dihydroergosterol II agree with those for a $\Delta^{8(14)}$ double bond, but, having regard to the preparation of this sterol by the reduction of ergosterol, or the so-called ergosterol F, under alkaline conditions, such a formulation would be unexpected. Indeed, since both α-dihydroergosterol (dihydroergosterol I) and dihydroergosterol II give the same substance on epimerisation (Windaus *et al.*, *Annalen*, 1931, **488**, 91), and since dihydroergosterol II shows very weak absorption at 2400 A. (Windaus *et al.*, *Annalen*, 1930, **477**, 268) and has a somewhat lower m. p. than α-dihydroergosterol, it is strongly implied that the sterol II is only a slightly impure form of the α-sterol. Accordingly it is assumed below that dihydroergosterol II and α-dihydroergosterol are identical. Dihydroergosterol III was thought to possess a Δ^{14}-unsaturated linkage (Dithmar and Achtermann, *Z. physiol. Chem.*, **1932**, **205**, 55; Heilbron, Johnstone, and Spring, *J.*, **1929**, 2248), but the optical rotatory power data are in complete disagreement with this formulation (the Δ values for the nuclear unsaturation of the sterol and its acetate are +71 and +76 respectively, whereas values of −24 and −20 are to be anticipated according to Table I). The reason for these anomalies is discussed further below.

TABLE IV.

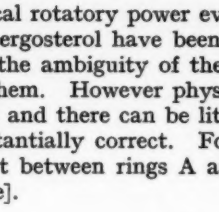
Substance.	Ⱶ positions.	Sterols. Δ values for both Ⱶ's.	Sterols. Ⱶ to be characterised.	Sterols. Δ value for other Ⱶ (ex tables).	Sterols. Δ value for characterised Ⱶ.	Acetates. Δ values for both Ⱶ's.	Acetates. Ⱶ to be characterised.	Acetates. Δ value for other Ⱶ (ex tables).	Acetates. Δ value for characterised Ⱶ.	Benzoates.* Δ values for both Ⱶ's.	Benzoates.* Ⱶ to be characterised.	Benzoates.* Δ value for other Ⱶ (ex tables).	Benzoates.* Δ value for characterised Ⱶ.	Ref.
Brassicasterol	5 : 6, 22 : 23	+308	22 : 23	+251	*+57*	+314	22 : 23	+243	*+71*	+244	22 : 23	+173	*+71*	1
Poriferasterol	5 : 6, 22 : 23	+310	22 : 23	+251	*+59*	+319	22 : 23	+243	*+76*	+237	22 : 23	+173	*+64*	1
Stigmasterol	5 : 6, 22 : 23	+298	22 : 23	+251	*+47*	+310	22 : 23	+243	*+67*	+233	22 : 23	+173	*+60*	1
Zymosterol	9 : 11, 24 : 25	− 99	24 : 25	−100	*+ 1*	− 85	24 : 25	− 77	*− 8*	− 92	24 : 25	−103	*+11*	1
Fucosterol	5 : 6, 24 : 28	+269	24 : 28	+251	*+18*	+273	24 : 28	+243	*+30*	+187	24 : 28	+173	*+14*	1
α-Dihydroergosterol	7 : 8, 22 : 23	+144	7 : 8	+ 61	*+83*	+114	7 : 8	+ 61	*+53*	+122	7 : 8	+ 61	*+61*	1
α-Spinasterol	7 : 8, 22 : 23	+112	7 : 8	+ 61	*+51*	+ 92	7 : 8	+ 61	*+31*	+103	7 : 8	+ 61	*+42*	1
Episterol	7 : 8, S.C.†	+ 60	S.C.	+ 77	*−17*	+ 45	S.C.	+ 57	*−12*	+ 17	S.C.	+ 64	*−47*	1
β-Spinasterol	7 : 8, S.C.	+ 75	S.C.	+ 77	*− 2*	+ 46	S.C.	+ 57	*−11*	+ 63	S.C.	+ 64	*− 1*	1
δ-Spinasterol	7 : 8, S.C.	+ 75	S.C.	+ 77	*− 2*	+ 64	S.C.	+ 57	*+ 7*	+ 47	S.C.	+ 64	*−17*	1
Ascosterol	9 : 11, S.C.	−115	S.C.	−100	*−15*	− 70	S.C.	− 77	*+ 7*	−119	S.C.	−103	*−16*	1
Faecosterol	9 : 11, S.C.	−103	S.C.	−100	*− 3*	− 61	S.C.	− 77	*+16*	− 99	S.C.	−103	*+ 4*	1
Dihydroergosterol II	N.‡, 22 : 23	+ 96	N.	+ 61	*+35*	+ 79	N.	+ 61	*+18*	—	—	—	—	1, 3, 8
Dihydroergosterol III	N., 22 : 23	+132	N.	+ 61	*+71*	+137	N.	+ 61	*+76*	—	—	—	—	1, 9, 10

* Includes dinitrobenzoates. † Side chain. ‡ Nuclear bond.

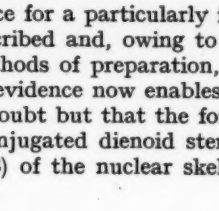
Table V correlates the optical rotatory power evidence for a particularly interesting class of compounds. A large number of isomers of ergosterol have been described and, owing to the lability of the conjugated dienoid systems involved and the ambiguity of the methods of preparation, it has been difficult to assign structures to the majority of them. However physical evidence now enables a clear differentiation of most of these isomers to be effected, and there can be little doubt but that the formulæ suggested for these substances in this paper are substantially correct. For conjugated dienoid sterols containing the two double bonds in different rings (except between rings A and B) of the nuclear skeleton five distinct formulæ are possible [(III) to (VII) inclusive].



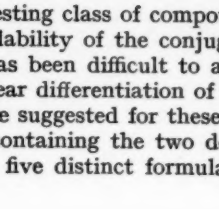
(III.)



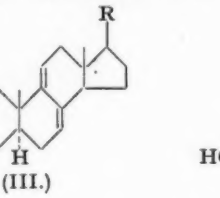
(IV.)



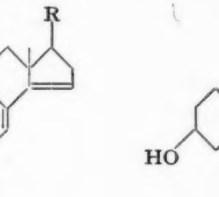
(V.)



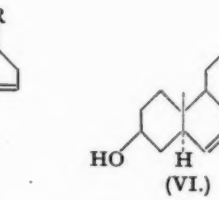
(VI.)



(VII.)



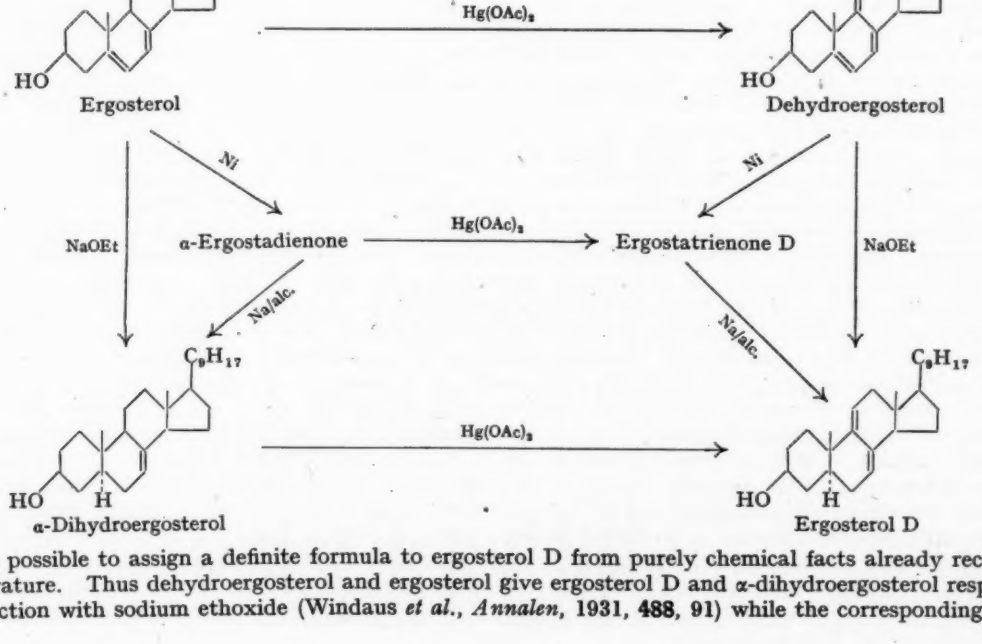
(VIII.)



(IX.)

The formula type (IV) for ergosterol B_3 and dehydrocholesterol B_3 is assigned because of the ease with which these sterols form maleic anhydride adducts, while all other compounds of the class under consideration [represented by (III), (V), (VI), (VII)] are without such affinity for philodienes. The formula (IV) for the B_3 sterols is supported by spectrographic evidence (see below), by the lead tetra-acetate experiments of Chen (*Ber.*, 1937, **70**, 1432), and by the parallel ease with which the comparable $\Delta^{8(14)}$-7 : 15-diketo system (Stavely and Bollenback, *J. Amer. Chem. Soc.*, 1943, **65**, 1285; compare the behaviour of amyradienedionol) forms a cyclic pyridazine derivative.

It has been the custom to formulate ergosterol D, one of the well-characterised ergosterol isomers, as (V; R = C_9H_{17}) (Callow, *J.*, 1936, 462) on the basis of the $\Delta^{8(14)}$ formula for its chemical progenitor, α-dihydroergosterol. Now that it has been conclusively shown that α-dihydroergosterol is not α-($\Delta^{8(14)}$) but γ-(Δ^{7}) olefinic, it is not surprising to find that optical rotatory power evidence definitely precludes the formula type (V) for ergosterol D.



It is possible to assign a definite formula to ergosterol D from purely chemical facts already recorded in the literature. Thus dehydroergosterol and ergosterol give ergosterol D and α-dihydroergosterol respectively on reduction with sodium ethoxide (Windaus *et al.*, *Annalen*, 1931, **488**, 91) while the corresponding ketones

are obtained by heating with metallic nickel (Windaus and Auhagen, *Annalen*, 1929, **472**, 185; Dithmar and Achtermann, *loc. cit.*). Ergosterol D derivatives are obtained also from the corresponding α-dihydroergosterol compounds by dehydrogenation with mercuric acetate (Heilbron, Johnstone, and Spring, *J.*, 1929, 2253; Windaus and Auhagen, *loc. cit.*; Windaus and Lüttringhaus, *Annalen*, 1930, **481**, 119). These interrelationships are more easily illustrated in the accompanying diagram and indicate strongly the correctness of (III) as the basic diene type for ergosterol D. The formulation receives additional support from the optical properties of the $\Delta^{7,9,22}$-ergostatrien-3(β) : 5-diol obtainable from dehydroergosterol (see Table V). The recently described cholestadiendiol (m. p. 228°) of Windaus *et al.* (*Annalen*, 1942, **552**, 135, 142) was formulated as a $\Delta^{7,9}$-diene. Such a formulation is quite contrary to the optical rotatory power evidence (Table V) and to the observed position of the ultra-violet absorption maximum at 2480 A. (see below).

Evidence in favour of the formula type (V) for dehydro-α-ergostenol is provided by general chemical reasoning (see below) and by the observed position of its ultra-violet absorption maximum. This maximum is at 2480 A. for both dehydro-α-ergostenol (Booker, Evans, and Gillam, *J.*, 1940, 1453) and for the analogous dehydro-α-cholestenol (Heath-Brown, Heilbron, and Jones, *J.*, 1940, 1482). Recently it has become widely accepted that increased substitution of a chromophore increases the wavelength of maximum absorption; within the range 2400—2500 A., which is characteristic of conjugated steroid dienes with two double bonds in different rings (Bergmann and Hirschmann, *J. Org. Chem.*, 1939, **4**, 40), this effect is readily apparent. Thus trisubstituted dienes, like $\Delta^{4,6}$-cholestadienol absorb at 2390 A. (Petrow, *J.*, 1940, 66; Spring and Swain, *ibid.*, 1941, 320), whilst the tetrasubstituted dienes ergosterol B_3 and ergosterol D have maxima at 2420 A. (Booker, Evans, and Gillam, *loc. cit.*; compare Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72); the pentasubstituted dienes dehydro-α-ergostenol and dehydro-α-cholestenol, formulated as above, fall logically into the sequence. Ergosterol B_1 has likewise an absorption maximum at 2480 A.; its Δ values for nuclear unsaturation are remarkably close to those for dehydro-α-ergostenol (Table V). Accordingly it is suggested that ergosterol B_1 is (V; $R = C_9H_{17}$), and that dehydro-α-ergostenol is its 22 : 23-dihydro-derivative.

The other two types of diene represented by (VI) and (VII) are not well defined. The representation of cholestadienol C as (VI; $R = C_8H_{17}$) (Windaus, Linsert, and Eckhardt, *Annalen*, 1938, **534**, 22) is probably incorrect as it is likely that the labile material described under this heading was non-homogeneous. It may well be that ergosterol B_2 and the cholestadiendiol, m. p. 228°, mentioned above, should be represented by (VI), there being no examples of (VII) extant. However the formula type (V) for the cholestadienediol is not excluded. The formulation of ergosterol B_2 as (VI; $R = C_9H_{17}$) is also supported by its method of formation (see below). All the substances now grouped under (VI) have absorption maxima at 2480 A. which probably reflect the unique position of one of the double bonds in the chromophore as exocyclic to a five-membered ring (compare Woodward, *loc. cit.*).

The optical rotatory power data for ergosterols E, F, and G (Table V) as well as spectrographic and chemical evidence already recorded in the literature show that the formulæ tentatively suggested by Sobotka (" The Chemistry of the Sterids," p. 252 *et seq.*) for these substances must be rejected. Space restrictions do not justify the presentation of the detailed reasoning here, but it is clear that ergosterols E and F are non-homogeneous whilst ergosterol G, although its Δ values agree with those for $\Delta^{5,14}$-nuclear unsaturation, may well be similarly impure. Two other diethenoid sterols, tetrahydrodehydroergosterol and $\Delta^{5,14}$-ergostadienol, show anomalous Δ values (Table V) and there are additional good reasons for suggesting that these substances, as well, are non-homogeneous. α_1-Sitosterol, too, cannot have the suggested 5 : 6 and 14 : 15 double bonds (Bernstein and Wallis, *J. Amer. Chem. Soc.*, 1939, **61**, 2308) as the Δ values observed on reduction are very different from those to be anticipated (+260 for the sterol and +257 for the acetate). This supports the discrepancy already noted between the assigned structure of this substance and its optical rotation (compare Bernstein, Wilson, and Wallis, *J. Org. Chem.*, 1942, **7**, 103) and tends to confirm its nature as triterpenoid. A further confirmation of the relationship between neosterol and ergosterol (Part I) and an additional disproval of the suggested analogy with *iso*dehydrocholesterol (Wieland, Rath, and Hesse, *loc. cit.*) are provided by the data in Table V. Judging by the molecular rotation of neosterol this substance consists of a mixed crystal of ergosterol with about 20% of α-dihydroergosterol (compare Callow, *Biochem. J.*, 1931, **25**, 87).

Table VI lists steroid hydrocarbons containing one or two nuclear double bonds. For the first type of hydrocarbon the Δ values observed are not greatly different from those recorded for the corresponding sterols (see Table I). The Δ value for the reduction of the nuclear double bond in α-ergostadiene corresponds best to that for Δ^7-unsaturation, rather than to that for the previously suggested $\Delta^{8(14)}$-unsaturation. The fact that α-ergostadiene gives ergostatriene D (double bonds at 7 : 8 and 9 : 11) on mercuric acetate dehydrogenation supports this formulation. However, the molecular rotation difference recorded for the reduction of the nuclear double bond in β-ergostadiene (Heilbron, Spring, and Webster, *J.*, 1932, 1705) is far removed from that expected, as is the comparable constant for its chemical progenitor dihydroergosterol III (β-dihydroergosterol : see above). Both of these substances show Δ values which are very much greater than those predicted from their suggested formulæ (β-ergostadiene has $\Delta = +142$ for its nuclear unsaturation, whereas a value of about −25 is to be anticipated). Both can be obtained by the hydrogen chloride induced isomerisation of Δ^7-unsaturated steroids and both can be reduced to the corresponding $\Delta^{8(14)}$ compounds (compare the smooth and complete reduction of sterols which really do possess Δ^{14} unsaturation). Now while $\Delta^{8(14)}$-sterols are well known to rearrange smoothly to the Δ^{14}-isomers by the catalytic action of hydrogen chloride, there is good reason to believe that Δ^7-compounds should furnish a mixture of the corresponding Δ^5- and Δ^{14}-sterols.

TABLE V.

Substance.	Suggested formula: literature.	Suggested formula: this paper.	$[M]_D$ Sterol etc. Sterol.	$[M]_D$ Sterol etc. Acetate.	Δ_1.	$[M]_D$ Sterol etc. Stanol.	$[M]_D$ Sterol etc. Acetate.	Δ values. Sterol.	Δ values. Acetate.	References.
Ergosterol D	(V; R = C_9H_{17})	(III; R = C_9H_{17})	+ 83	+ 96	*+ 13*	+ 64	+ 27	*− 80* ¶	*− 130* ¶	1, 8, 11, 12, 13, 14
epi-Ergosterol D *	(V; R = C_9H_{17})	(III; R = C_9H_{17})	+135	+197	*++ 62*	++ 56	++ 93	*− 140* ¶	*− 165* ¶	8, 15, 16
$\Delta^{7,9,22}$-Ergostatrien-3(β): 5-diol †	(III; R = C_9H_{17})	(III; R = C_9H_{17})	+198	+221	*++ 23*	++ 77 ‡	++ 54 ‡	*− 182* ¶	*− 228* ¶	16, 17
Dehydrocholesterol B_3	(IV; R = C_9H_{17})	(IV; R = C_9H_{17})	−561	−490	*+ 71*	++ 93	+ 60	*+654*	*+550*	1, 18
Ergosterol B_3	(IV; R = C_9H_{17})	(IV; R = C_9H_{17})	−792	−832	*− 40*	++ 64	++ 27	*+795* ¶	*+798* ¶	1, 8, 13, 19
Dehydro-α-cholestenol	(V; R = C_8H_{17})	(V; R = C_8H_{17})	− 35	—	—	++ 93	—	*+128*	—	1, 20
Dehydro-α-ergostenol	(V; R = C_9H_{19})	(V; R = C_9H_{19})	− 67	−135	*− 68*	++ 64	++ 27	*+131*	*+162*	1, 5, 11, 14, 21
Ergosterol B_1	—	(V; R = C_9H_{17})	−166	−241	*− 75*	++ 64	++ 27	*+169* ¶	*+207* ¶	1, 8, 9
Cholestadienol C	(? VI; R = C_8H_{17})	Impure	− 11	—	—	+ 93	—	*+104*	—	1, 22
$\Delta^{6,8(14)}$-Cholestadien-3(β): 9-diol §	(VI; R = C_8H_{17})	(VI; R = C_8H_{17})	− 80	− 80	*± 0*	—	—	—	—	22
Ergosterol B_2	—	(VI; R = C_9H_{17})	−349	−350	*− 1*	+ 64	+ 27	*+352* ¶	*+316* ¶	1, 8
$\Delta^{7,9}$-Cholestadien-3(β): 6-diol ‖	(III; R = C_9H_{17})	(? VI; R = C_9H_{17})	−203	—	—	+140 ††	—	*+343*	—	23, 24, 25
Ergosterol E	(VII; R = C_9H_{17})	Impure	− 91 **	−166 **	*− 75*	++ 64	++ 27	*+ 94* ¶	*+132* ¶	1, 26, 30
Ergosterol F	(VI; R = C_9H_{17})	Mixture	− 79	−105	*− 26*	++ 64	++ 27	*+ 82* ¶	*+ 71* ¶	1, 16, 30
Ergosterol G	(VIII; R = C_9H_{17})	See text	−206	−276	*− 70*	+++ 64	++ 27	*+209* ¶	*+242* ¶	1, 27, 30
Tetrahydrodehydroergosterol ...	—	Mixture	− 52	− 40	*+ 12*	++ 64	++ 27	*+116*	*+ 67*	1, 28
$\Delta^{5,14}$-Ergostadienol	F's at 5 : 6 and 14 : 15	Impure	−115	−154	*− 39*	++ 64	++ 27	*+179*	*+181*	1, 29
α_1-Sitosterol	F's at 5 : 6 and 14 : 15	Triterpenoid	− 8	+132	*+140*	+112	+179	*+120*	*+ 47*	1
iso-Dehydrocholesterol	(VIII; R = C_8H_{17})	(VIII; R = C_8H_{17})	− 69	− 47	*+ 22*	+ 93	+ 60	*+162*	*+107*	1
Neosterol	(VIII; R = C_9H_{17})	(IX; R = C_9H_{17})	−416	−294	*+122*	++ 64	++ 27	*+419* ¶	*+260* ¶	1

* The –OH at C_3 is, of course, in the (α) position in this substance.
† This substance has an additional –OH at the 5 position.
†† These data are for 3 : 5-dihydroxycholestane and are unlikely to be far removed from those for the corresponding ergostane compound.
‡ This substance has an additional –OH at the 9 position.
§ This substance is said to possess an additional –OH at the 6 position.
‖ Corrected for side chain reduction (subtract 61).
¶ These rotations are for the 5461 A. line.
** The value for cholestan-6-ol was used for this calculation: in general there is no difference between the molecular rotations of hydrocarbons and the corresponding sterols with a (β)-ol grouping at the 3 position.

TABLE VI.

Substance.	F's to be characterised.	$[M]_D$. Unsaturated hydrocarbon.	$[M]_D$. Corresponding saturated hydrocarbon.	Δ value.	References.
Δ^2-Cholestene	2 : 3 *	+241	+89	−152	20, 31, 32, 33, 34, 35, 36, 37, 38
Δ^4-Cholestene	4 : 5	+248	+89	−159	20, 31, 32, 33, 34, 35, 39, 40
Δ^5-Cholestene	5 : 6	−207	+89	+296	20, 31, 32, 33, 34, 35, 41
Δ^6-*i*-Cholestadiene	6 : 7	−225	+93 †	+318	35, 42, 43
α-Ergostadiene	7 : 8	− 38	+77	+ 54 ‡	21, 44, 45, 46, 47
Δ^8-Cholestene	? 8 : 9	+ 41 §	+89	+ 48	20, 31, 32, 33, 34, 35, 48
α-Cholestene	8 : 14	+ 78 §	+89	+ 11	20, 31, 32, 33, 34, 35, 48
α-Ergostene	8 : 14	+ 42	+77	+ 35	21, 44, 45, 46, 47
β-Cholestene	14 : 15	+100 §	+89	− 11	20, 31, 32, 33, 34, 35, 48
β-Ergostene	14 : 15	+ 81	+77	− 4	21, 44, 45, 46, 49
$\Delta^{2,4}$-Cholestadiene	2 : 3, 4 : 5	+486	+89	−397	20, 31, 32, 33, 34, 35, 50
$\Delta^{3,5}$-Cholestadiene	3 : 4, 5 : 6	−460	+89	+549	20, 31, 32, 33, 34, 35, 37, 39, 51
$\Delta^{4,6}$-Cholestadiene	4 : 5, 6 : 7	+ 15	+89	+ 74	20, 31, 32, 33, 34, 35, 52
7-Dehydrocholestene	5 : 6, 7 : 8	−467	+89	+556	20, 31, 32, 33, 34, 35, 53
Ergostatriene D	7 : 8, 9 : 11	+163	+77	−147 ‡	21, 44, 45, 46, 47
$\Delta^{7,14}$-Cholestadiene	7 : 8, 14 : 15	−342 §	+89	+431	20, 31, 32, 33, 34, 35, 54
$\Delta^{8,14}$-Cholestadiene	8 : 9, 14 : 15	− 81 §	+89	+170	20, 31, 32, 33, 34, 35, 54
Dehydro-α-ergostene	8 : 9, 14 : 15	− 57	+77	+134	21, 44, 45, 46
Anomalous.					
β-Ergostadiene	?14 : 15	−126	+77	+142 ‡	21, 44, 45, 46, 47
$\Delta^{6,8(14)}$-Cholestadiene	? 6 : 7, 8 : 14	+ 4 §	+89	+ 85	20, 31, 32, 33, 34, 35, 54
$\Delta^{7,9}$-Cholestadiene	? 7 : 8, 9 : 11	+114 §	+89	− 25	20, 31, 32, 33, 34, 35, 54

* For evidence in favour of this double bond position see References 38 and 70.

† The value for *i*-cholesterol is used here; it is unlikely to be very far removed from that of the unknown *i*-cholestene.

‡ Corrected for side chain reduction.

§ These rotations in CCl_4; there is probably very little difference between these values and the true values in chloroform (see Eck and Thomas, References 55 and 56).

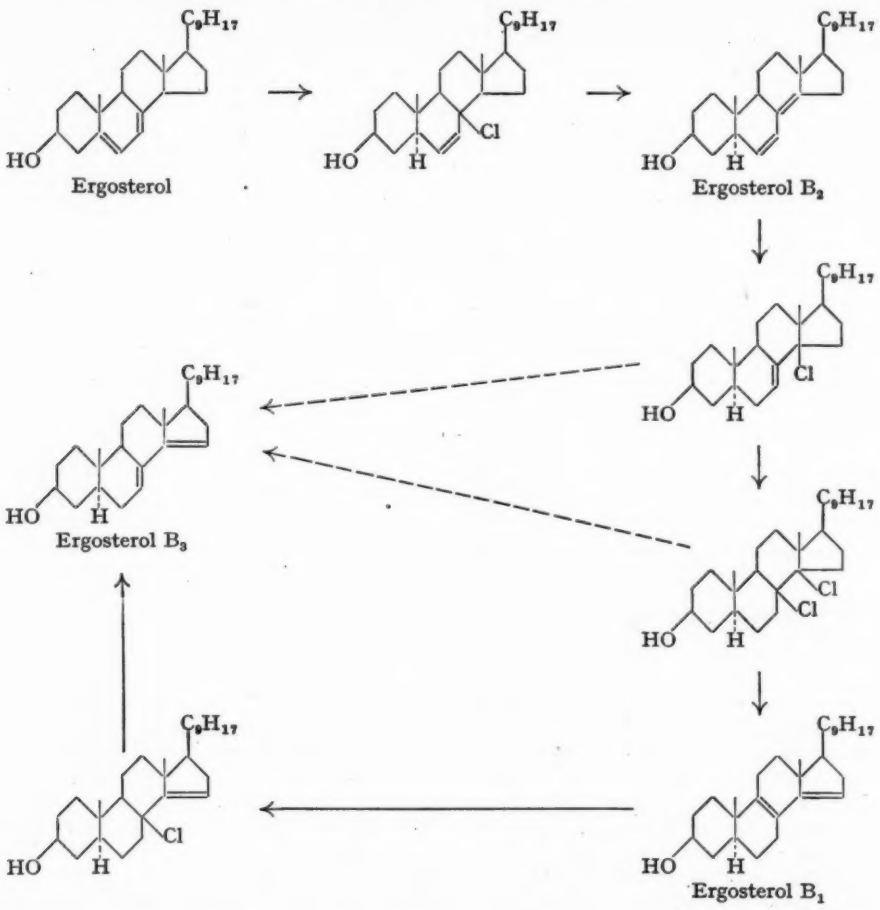
Thus zymostenol, which has one double bond in the ϵ- or Δ^9-position, furnishes a mixture of cholesterol and β-cholestenol on isomerisation with hydrogen chloride (Wieland and Benend, *Ber.*, 1942, **75**, 1708) and zymosterol itself behaves in an excatly similar manner (Wieland, Rath, and Benend, *Annalen*, 1942, **548**, 19). The presence of a substantial proportion of the Δ^5-steroid in dihydroergosterol III and β-ergostadiene, as well as a certain amount of the unrearranged material, would, of course, readily explain the unexpectedly high Δ values on reduction (compare Table I), and this interpretation of the behaviour of these compounds is suggested here as the reason for the optical anomalies observed.

Of the hydrocarbons containing two nuclear conjugated double bonds, the recently described cholestadienes of Eck and Hollingsworth (*J. Amer. Chem. Soc.*, 1942, **64**, 140) have values which, except in the case of $\Delta^{8,14}$-cholestadiene (dehydro-α-cholestene), are only roughly similar to those for the corresponding sterols. On the other hand the Δ values for 7-dehydrocholestene, dehydro-α-ergostene, and ergostatriene D are in good agreement with those for their respective sterol types (compare Table V). Of these cholestadienes the rotation for the $\Delta^{7,14}$ compound indicates that the material is, indeed, substantially of the assigned type, while the Δ values for the $\Delta^{6,8(14)}$- and $\Delta^{7,9}$-cholestadienes are, in proportion, far removed from those expected. Before discussing these further, it is desirable to give some explanation of the various methods of diene synthesis for steroids with the conjugation between two different rings (excepting between rings A and B) of the nucleus.

Three general classifications can be made. (A) Rearrangement of preformed diene systems. It is in this way that ergosterols B_1, B_2, and B_3 are formed (Windaus *et al.*, *Annalen*, 1931, **488**, 91) by the hydrogen chloride induced isomerisation of ergosterol itself. The reactions can be formulated as proceeding by 1 : 2 or 1 : 4 addition and 1 : 2 elimination as in the diagram. In this way the formation of ergosterol B_3 from ergosterols B_1 and B_2 is readily explained (Windaus *et al.*, *loc. cit.*). (B) Direct dehydrogenation by mercuric acetate, apparently without double bond migration. Examples have already been given above. (C) Reactions proceeding by hydroxylation of a double bond followed by two-stage elimination, or elimination, allylic rearrangement, and further elimination. Examples are shown in the diagram for the hydroxylated compounds, but exactly similar mechanisms can be postulated with bromine, etc.

Both the $\Delta^{7,9}$- and the $\Delta^{6,8(14)}$-cholestadienes mentioned above were synthesised by methods that cannot be reconciled with any of these classifications. Thus the $\Delta^{7,9}$-diene is said to be prepared by the action of mercuric acetate on $\Delta^{8(9)}$-cholestene (the preparation using bromine cannot be criticised on these grounds). However, if the $\Delta^{8(9)}$-cholestene is substantially Δ^7-cholestene as previously suggested (Part I) the discrepancy is clearly resolved. Probably, in actual fact, the so-called $\Delta^{8(9)}$-cholestene is a mixture in which the Δ^7-isomer is predominant. Eck and Hollingsworth (*loc. cit.*) describe the preparation of the $\Delta^{6,8(14)}$-cholestadiene by the action of alcoholic hydrochloric acid on $\Delta^{8(9)}$-cholesten-7-ol, a reaction which should, according to the above classification, furnish the already mentioned $\Delta^{7,9}$-isomer. However, the identity of $\Delta^{8(9)}$-cholesten-7-ol

itself is by no means proved, as its structure depends on the correctness of the formulation of $\Delta^{8(9)}$-cholesten-7-one. This ketone is said to possess a specific rotation of +4° (Eck and Hollingsworth, *J. Amer. Chem. Soc.*,



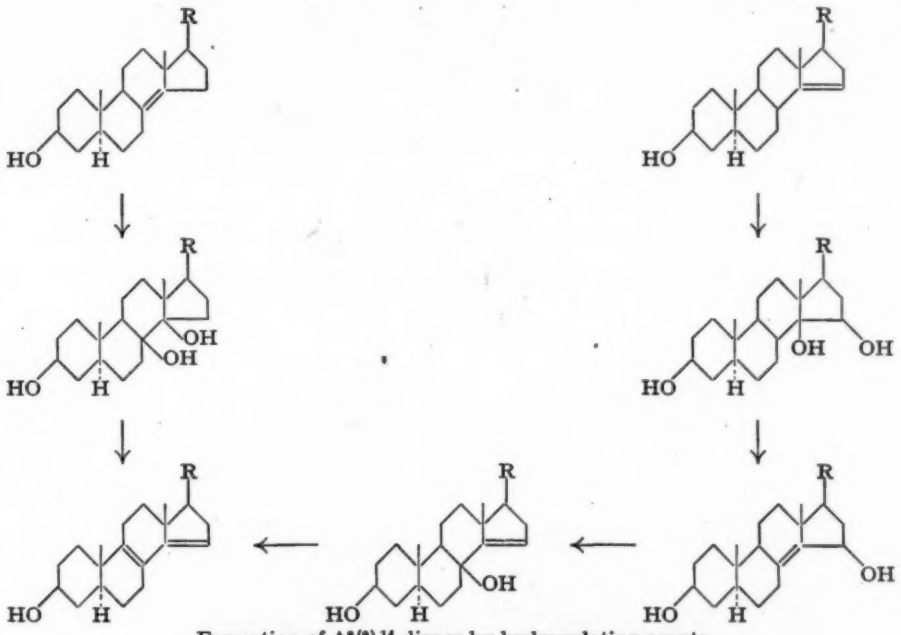
1941, **63**, 2986), so that the molecular rotation difference with respect to cholestane is +74. The exactly analogous $\Delta^{8(9)}$-7-keto compounds of Stavely and Bollenback (*ibid.*, 1943, **65**, 1290, 1600) have, however, marked specific lævorotations (of the order −40°) and Δ values of +192 ± 15. It would be unwise therefore to consider the $\Delta^{7,9}$- and $\Delta^{6,8(14)}$-cholestadienes to be chemical individuals until further evidence as to their purity is available.

TABLE VII.

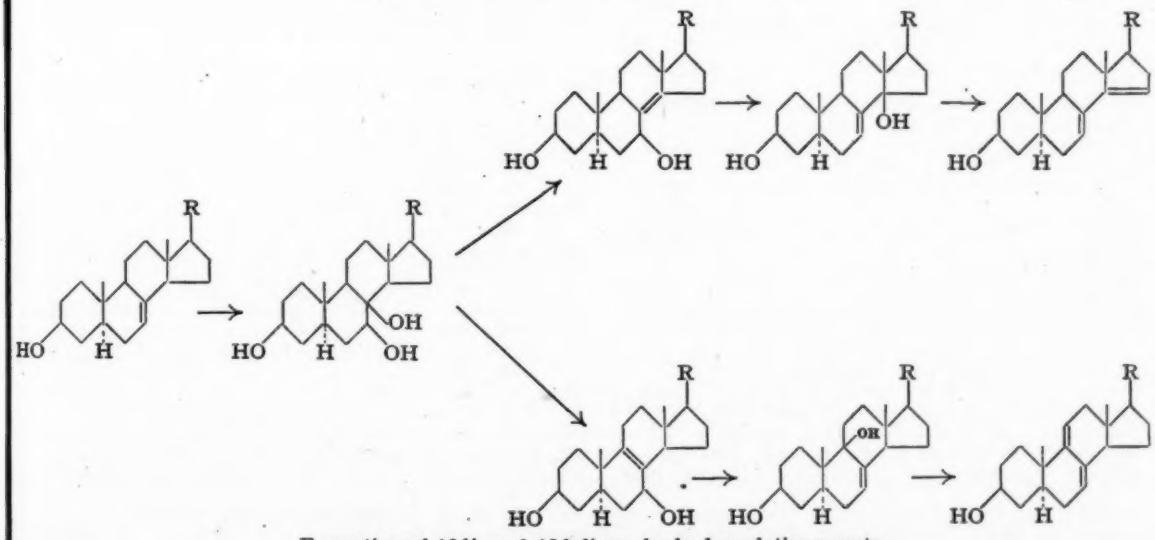
Diene type.	Position of ⊢'s.	Δ values of ⊢'s. First.	Second.	Sum.	A.M. of diene Δ values (ex tables).	No. of examples.	Limits of variation from A.M.	References.
$\Delta^{2,4}$-Stadienes	2 : 3, 4 : 5	−152	−159	−311	−397	1	—	20, 31, 32, 33, 34, 35
$\Delta^{3,5}$-Stadienes	3 : 4, 5 : 6	−101 *	+251	+150	+549	1	—	20, 31, 32, 33, 34, 35, 69
$\Delta^{4,6}$-Stadienes	4 : 5, 6 : 7	−159	+200 *	+ 41	+ 74	1	—	20, 31, 32, 33, 34, 35
$\Delta^{5,7}$-Stadien-3(β)-ols ...	5 : 6, 7 : 8	+251	+ 77	+328	+538	5	+40 to −40	1
$\Delta^{6,8}$-Stadien-3(β)-ols ...	6 : 7, 8 : 9	+200 *	+ 48	+248	+162	1	—	1
$\Delta^{6,8(14)}$-Stadien-3(β)-ols	6 : 7, 8 : 14	+200 *	+ 9	+209	+352	1	—	1
$\Delta^{7,9}$-Stadien-3(β)-ols ...	7 : 8, 9 : 11	+ 77	−100	− 23	−134	3	+54 to −48	1
$\Delta^{7,14}$-Stadien-3(β)-ols ...	7 : 8, 14 : 15	+ 77	− 24	+ 53	+725	2	+70 to −71	1
$\Delta^{8,14}$-Stadien-3(β)-ols ...	8 : 9, 14 : 15	+ 48	− 24	+ 24	+143	3	+26 to −15	1

* These values have been assigned. That for the Δ^{3}-bond is calculated from the molecular rotations recorded for Δ^{3}-cholesten-3 : 4-diol (Reference 34) and the *trans*-cholestan-3 : 4-diol of Rosenheim and Starling (Reference 69). The value for the Δ^{6}-bond is certainly of the right sign and probably of the right magnitude. Compare the rotations of Δ^{6}-*i*-cholestadiene and Δ^{6}-cholesten-3(β) : 5-diol (References 57 and 58).

The correlation of the optical rotatory power data on sterol dienes has led to the development of an interesting rule, which enables a clear prediction to be made as to whether the rotation of the diene will be less or greater than that of the corresponding saturated analogue. The operation of this generalisation, which may be called the " dichromophore rule," is illustated in Table VII. This rule states that, for any sterol containing two unit chromophores in conjugation, the algebraic sum of the Δ values for the two individual



Formation of $\Delta^{8(9),14}$-dienes by hydroxylating agents.



Formation of $\Delta^{7,14}$- and $\Delta^{7,9}$-dienes by hydroxylating agents.

chromophores is always of the same sign and often of the same magnitude as the Δ value for the transformation of the conjugated dichromophore to its saturated analogue. This generalisation is equally applicable to αβ-unsaturated ketones (Table VIII), although there is one exception which, it is suggested, is due to serious impurity. In all cases save two the Δ values for the conjugated dichromophore is greater than the sum of the Δ values for the individual chromophores and this fact may prove to be a further extension of the scope of the rule. The generalisation cannot be extended to three chromophores in straight conjugation, but is valid for all the examples so far listed in the sterol field of three chromophores in cross-conjugation.

The possible operation of " vicinal action " in affecting the optical rotatory powers of the compounds mentioned in this paper will be discussed in a further communication.

TABLE VIII.

Unsaturated ketone type.	Δ values for individual chromophores.	F.	Δ values for individual chromophores. Ketone.	Sum.	A.M. of dichromophore Δ values.	No. of examples.	Limits of variation from A.M.	References.
Δ^{1}-3-Ketones	—		− 69	—	−161	1	—	1, 59, 60
Δ^{4}-3-Ketones	−159		− 69	−228	−259	2	+9 to −9	1
Δ^{4}-6-Ketones *	− 78 †		+153	+ 75	+145	1	—	1, 57, 61, 68
Δ^{5}-7-Ketones ‡	+243		+220	+463	+489	1	—	1, 62
Δ^{8}-7-Ketones ‡	± 0		+220	+220	+192	2	+15 to −15	1, 63, 64
$\Delta^{8(14)}$-7-Ketones ‡	+ 9		+220	+229	+318	3	+16 to −16	1, 63, 64, 65, 66
$\Delta^{8(14)}$-15-Ketones ‡	+ 9		—	—	−462	2	+1 to ±0	1, 66, 67
Anomalous.								
3 : 7-Diketo-$\Delta^{8(14)}$-ergosten-5-ol	+ 24		+220	+244	−193 §	—	—	1, 29

* Values for the 3(β)-ol derivatives.
† This value is calculated using the molecular rotation of *allo*-cholesterol (Reference 68) in C_6H_6.
‡ Values for the 3(β) acetates.
§ Calculated using the recorded molecular rotation of 3 : 5-dihydroxycholestane (Reference 17).

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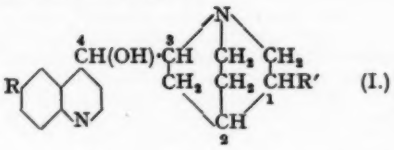
102. *Conversion of Hydroquinidine into Hydrocinchonine and of Cupreine into Cinchonidine.*

By Harold King.

The aim of this investigation was the removal of the methoxyl groups from the methoxylated cinchona alkaloids by a mild method which would leave the stereochemical structure intact. This has been accomplished for dihydroquinidine and cupreine by an application of the Bucherer reaction. The former base yields dihydrocinchonine and the latter cinchonidine. The classification of the eight main cinchona alkaloids on a stereochemical basis by King and Palmer (*J.*, 1922, **121**, 2580) is supported.

King and Palmer (*loc. cit.*) proposed a classification of the natural cinchona alkaloids depending on the optical contribution of the four asymmetric centres present to the observed rotation. On this system the main cinchona alkaloids and their dihydro-derivatives (I)



(I.)

were classified as follows :

Alkaloid.	Optical sign of— C1 with C2.	C3.	C4.
Cinchonine (R = H; R′ = CH:CH$_2$) and Dihydrocinchonine	+	+	+
Cinchonidine (R = H; R′ = CH:CH$_2$) and Dihydrocinchonidine	+	−	−
Quinine (R = OMe; R′ = CH:CH$_2$) and Dihydroquinine	+	−	−
Quinidine (R = OMe; R′ = CH:CH$_2$) and Dihydroquinidine	+	+	+

This classification was accepted by Rabe (*Annalen*, 1932, **492**, 242) with a greater wealth of experimental results. Henry, Solomon, and Gibbs (*J.*, 1937, 592) and Solomon (*J.*, 1938, 6) have expanded the classification by furnishing experimental evidence which enabled them to suggest signs for the optical contribution of each of the carbon atoms C1 and C2, a subject also dealt with more recently by Prelog and Zalan (*Helv. Chim. Acta*, 1944, **27**, 535). Emde (*ibid.*, 1932, **15**, 557), however, questioned the above classification and preferred to regard the spatial arrangement around C1, C2, and C3 as identical in all the natural bases, the isomerism between cinchonine and cinchonidine, for instance, being solely dependent on the different spatial arrangement around C4.

On either system quinine and dihydroquinine should be the methoxylated derivatives of cinchonidine and dihydrocinchonidine respectively, and quinidine and dihydroquinidine should be the methoxylated derivatives of cinchonine and dihydrocinchonine respectively. Apart from the regularities in the rotations on which this classification is based there is no experimental evidence in support of this view. The present communication furnishes a proof of these relationships.

For the replacement of the methoxyl group of the methoxylated cinchona alkaloids by hydrogen, the process used by O. Fischer (*Chem. Soc. Abstr.*, 1901, i, 405) for conversion of harmine *via* harmol into aminoharman by heating harmol at 250° with zinc chloride and ammonia seemed too drastic. In recent years considerable success has attended the application of the Bucherer reaction to hydroxyquinolines. Thus Woroshtzow and Kogan (*Ber.*, 1932, **65**, 142) were able to convert 6- and 8-hydroxyquinolines in good yield into the corresponding aminoquinolines by ammonium sulphite solution at 150°. Renfrew, Carlson, and Cretcher (*J. Amer. Chem. Soc.*, 1943, **65**, 2309) have also converted apocupreine (an isomeride of demethylated quinine) into derivatives of aminoapocinchonidine in a workable yield at 160°. Finally C. F. Boehringer and Soehne (D.R.P. 720,160) have patented the preparation of 6-aminodihydrocinchonine and 6-aminodihydrocinchonidine by allowing hydrocupreidine or hydrocupreine respectively to react with ammonium sulphite in presence of aqueous ammonia and water-soluble organic solvents at an elevated temperature.

A number of trial experiments along the lines of this patent were carried out on hydrocupreidine (demethylation product of hydroquinidine) and it was found that it could be converted into an aromatic amino-derivative by dissolving in ethylene glycol and heating to 150° with ammonium sulphite solution. The amino-compound was not very stable and did not crystallise as base or as a salt with the acids so far tried. It formed a soluble salt with sulphuric acid which could be diazotised and which on treatment with hypophosphorous acid by Mai's method (*Ber.*, 1902, **35**, 162) gave a workable yield of crystalline dihydrocinchonine identical in the melting point of the base and the dihydrobromide and in the optical rotation with an authentic specimen of natural dihydrocinchonine.

Through the generosity of Mr. Bernard F. Howard, Managing Director of Howards & Sons, Ilford, I was presented with a small specimen of cupreine first isolated by Howard and Hodgkin (*J.*, 1882, **41**, 16) from Cuprea bark. Cupreine on methylation gives quinine and thus is a phenolic alkaloid with a vinyl side-chain. It was of interest to apply the Bucherer reaction to this base under similar conditions. It readily gave an amino-base, soluble in dilute sulphuric acid, which could be diazotised and reduced by Mai's method to cincho-

nidine, identified as base and dihydrobromide by comparison with an authentic specimen of natural cinchonidine and its dihydrobromide.

It follows from these results that quinine and quinidine and their dihydro-derivatives are the methoxy derivatives respectively of cinchonidine and cinchonine and their dihydro-derivatives, a result consistent with the original classification of King and Palmer.

Experimental.

Conversion of Hydroquinidine into Hydrocinchonine.—Hydrocupreidine (1 g.) prepared by demethylation of pure hydroquinidine by the method of Heidelberger and Jacobs (*J. Amer. Chem. Soc.*, 1919, **41**, 817) was dissolved in ethylene glycol (2 c.c.) by warming, and the solution cooled. Aqueous ammonia (7·5 c.c., 20%) was then added followed by ammonium bisulphite solution (7·5 c.c.) prepared by passing excess of sulphur dioxide into cold aqueous ammonia (20%). The mixture was heated in a sealed Pyrex tube at 150° for 7·5 hours. The contents of 6 such tubes were filtered, the main bulk of the amorphous amino-base being insoluble. The filtrate was made strongly alkaline by addition of 50% sodium hydroxide solution and extracted three times with chloroform. The amorphous solid which had been filtered off was ground in a mortar and treated with the combined chloroform extracts in the presence of 2N-sodium hydroxide. Two clear solutions usually resulted, the upper dark coloured aqueous alkaline solution containing some unchanged hydrocupreidine. The chloroform was separated and the alkaline solution extracted several times with chloroform to remove all non-phenolic base. The combined chloroform extracts were washed with a little 2N-sodium hydroxide and finally with water and then distilled, the last small volume of chloroform being removed under reduced pressure. The residue of crude 6-aminodihydrocinchonine (2·22 g.) was dissolved in N-sulphuric acid (21·4 c.c.; 3 equiv.), cooled to 0°, and diazotised by addition of a solution of sodium nitrite (0·52 g.) in water (5 c.c.). The clear solution was then run fairly rapidly into hypophosphorous acid (50 c.c., 30%) previously cooled to 0° and kept at 0° for 24 hours. There was no noticeable evolution of nitrogen. The solution was treated with 2N-ammonia (125 c.c.) and chloroform (100 c.c.) and the dihydrocinchonine extracted completely by 5 further chloroform extractions (each 50 c.c.). The combined chloroform extracts were evaporated and left a crystalline base (1·75 g.). This was boiled with alcohol (5 c.c.) and gave dihydrocinchonine (0·85 g.). It was crystallised once more from absolute alcohol (40 c.c.), and separated in needles, m. p. 265° not depressed by an authentic specimen of natural dihydrocinchonine which melted at 266° (Found: C, 77·1; H, 8·2. Calc. for $C_{19}H_{24}ON_2$: C, 77·0; H, 8·2%). In N/10-hydrobromic acid (*c*, 0·235) it had $[\alpha]_D^{18°}$ + 220·4°. A specimen of authentic dihydrocinchonine under comparable conditions (*c*, 0·234) had $[\alpha]_D^{23°}$ + 219·7°. Emde (*loc. cit.*) gives $[\alpha]_D^{20}$ + 142° for the dihydrobromide whence for the base $[\alpha]_D^{20°}$ + 219·5° in agreement with the above figures. The dihydrobromide was recovered from each preparation and each specimen crystallised in hexagonal plates, m. p. 284—286° (decomp.), a mixture showing identical behaviour.

Conversion of Cupreine into Cinchonidine.—Cupreine (0·8 g.) was dissolved in warm ethylene glycol (2 c.c.) and the solution was cooled and treated with aqueous ammonia (7·5 c.c., 20%) followed by aqueous ammonium bisulphite (7·5 c.c.). The mixture was heated at 150° for 7·5 hours in a sealed tube. The contents of two such tubes were worked up for amino-base as described above, yield 0·6 g. The amino-base was dissolved in N-sulphuric acid (7·5 c.c.) and diazotised at 0°, and the solution was then run into hypophosphorous acid (30 c.c., 30%) also kept at 0°. After keeping for 48 hours at 0° the base was liberated by ammonia and extracted with chloroform. On removal of the solvent the base crystallised (0·56 g.). It was twice crystallised from benzene and separated in needles, m. p. 201°, undepressed by an authentic specimen of cinchonidine which melted at 202°. The dihydrobromide separated from water in tablets as a dihydrate (Found: C, 45·8; H, 5·8; H_2O, 7·8. Calc. for $C_{19}H_{22}ON_2,2HBr,2H_2O$; C, 46·3; H, 5·3; $2H_2O$, 7·3%). In N/10-hydrobromic acid (*c*, 0·421) the anhydrous salt had $[\alpha]_D^{19°}$ − 110° whence for the base $[\alpha]_D^{19}$ − 170·1°. A specimen of natural cinchonidine dihydrobromide was prepared. It crystallised similarly in tablets as a dihydrate, for the anhydrous salt of which $[\alpha]_D^{19°}$ − 109·9° (*c*, 0·4) whence for the base $[\alpha]_D^{19°}$ − 170·1°.

Emde (*loc. cit.*) describes the dihydrobromide as a monohydrate, which for the anhydrous salt had $[\alpha]_D^{20°}$ − 112·5°, whilst Buttle, Henry, and Trevan (*Biochem. J.*, 1934, **28**, 430) describe the hydrobromide as a dihydrate with $[\alpha]_D$ − 111·4° for the anhydrous salt. Both these values are in substantial agreement with those now recorded. Both salts melted at 268° (decomp.) alone or in admixture.

Ethylene glycol may possess some advantages for the crystallisation of the cinchona alkaloids since both hydrocupreidine and cupreine readily crystallise from this solvent.

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103. *Aminosteroids. Part I. α- and β-Forms of 7-Aminocholesterol.*

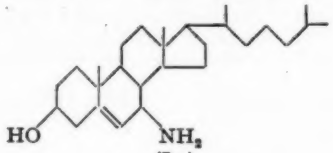
By Jean Barnett, Brenda E. Ryman, and F. Smith.

The α- and *β-isomers* of 7-aminocholesterol have been isolated by fractional crystallisation of the mixture obtained by reduction of the oxime of 7-ketocholesteryl acetate. The isomeric acetyl derivatives have also been separated, but all attempts to hydrolyse them to the free bases have failed. *α-7-Aminocholestanol* has been obtained by catalytic reduction of α-7-aminocholesterol. Both the α- and β-7-aminocholesterol isomers show high antibacterial activity *in vitro* against Gram-positive organisms, but no appreciable difference has been observed between the activities of the two spatial isomers.

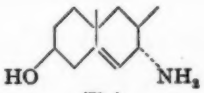
The preparation of various aminosterols was undertaken with a view to examining their activity as antibacterial agents. 7-Aminocholesterol (I) was chosen as the first member of the series to be examined, since it had already been made, in the form of a mixture of α- and β-isomers, by reduction of the oxime of 7-ketocholesteryl acetate with sodium in alcohol (Eckhardt, *Ber.*, 1938, **71**, 461). Eckhardt described the separation of the α- and β-*N*-acetyl derivatives by fractional crystallisation but did not succeed in separating the free bases. The above work has now been repeated; the two *N*-acetyl derivatives obtained by fractional crystallisation have been found to have melting points somewhat higher than those described by Eckhardt. It was not found possible to hydrolyse the *N*-acetyl compounds to the free bases, for alkaline conditions left the *N*-acetyl group untouched and acid treatment either effected no change or removed the amino group com-

pletely. However, the free aminosterols were eventually separated by direct fractional crystallisation from methyl alcohol–acetone. The mixture of isomers was first partially separated by elution from a column of alumina, by which means a seed crystal of the pure β-form was obtained. Since the latter is the less soluble of the two forms, it could be almost completely removed first by careful fractional crystallisation and the α-form could then be isolated from the mother liquors.

The nomenclature adopted here for the 7-amino-isomers is that corresponding to the 7-*N*-acetyl derivatives to which they give rise respectively, following Eckhardt's arbitrary designation for the latter (*loc. cit.*).



(Ia.)



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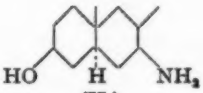

(II.)

α-7-*Aminocholesterol* (Ia) crystallises from methyl alcohol–acetone in diamond shaped prisms, m. p. 183—185°, $[\alpha]_D^{20°}$ −327° in chloroform. The β-*form* (Ib) crystallises as cubes or rectangular plates, m. p. 198—199°, $[\alpha]_D^{20°}$ +181° in chloroform. The conversion of both isomers into the corresponding *N*-acetyl derivatives having the melting points and rotations already found for the separated isomers confirms the completeness of the separation. The optical rotation of α-7-aminocholesterol appears to be one of the highest values recorded for any steroid.

The free aminosterols are sufficiently strong bases to take up carbon dioxide from the air; all crystallisations and filtrations were therefore carried out in an atmosphere of nitrogen. The bases can be precipitated quantitatively as their hydrochlorides by addition of dry ethereal hydrogen chloride to their solutions in ether. The salts are insoluble in water but are not precipitated from alcoholic solution by addition of water, soap-like, colloidal solutions being obtained (see also Eckhardt, *loc. cit.*).

The α- and β-7-aminocholesterol isomers have been catalytically reduced, in glacial acetic acid solution in the presence of platinum black, to the corresponding α- and β-7-aminocholestanol isomers. Of these, only the α-form (II) (analysed as the *hydrochloride*) has been obtained crystalline.

Biological results. Substances for testing were in the form of their hydrochlorides, made up in a 10% alcoholic solution. Dilutions of from 1 : 10^3 to 1 : (5 × 10^5) were tested in synthetic medium, glucose broth, and serum broth, against *Streptococcus hæmolyticus*, *Staphylococcus aureus*, *B. coli*, and *Ps. pyocyanea*. Results are shown in the Table.

Limiting dilution giving complete inhibition of growth.

Organism.	*Staph. aur.*	*Strep. hæm.*	*B. coli.*	*Ps. pyoc.*
Synthetic medium.				
α-7-Aminocholesterol	1 : (5 × 10^5)	1 : 10^5	1 : 10^3	nil.
β-7-Aminocholesterol	1 : (5 × 10^5)	1 : (5 × 10^5)	nil.	nil.
Mixed α- and β-isomers	1 : 10^5	1 : 10^5	nil.	nil.
α-7-Aminocholestanol	1 : 10^5	1 : (5 × 10^5)	1 : 10^3	nil.
Glucose broth.				
α-7-Aminocholesterol	1 : 10^5	1 : 10^5	nil.	nil.
β-7-Aminocholesterol	1 : 10^5	1 : (5 × 10^5)	nil.	nil.
Mixed α- and β-isomers	1 : 10^5	1 : 10^5	nil.	nil.
α-7-Aminocholestanol	1 : (5 × 10^4)	1 : (5 × 10^4)	nil.	nil.
Serum broth.				
α-7-Aminocholesterol	1 : 10^4	1 : 10^5	nil.	nil.
β-7-Aminocholesterol	1 : 10^4	1 : 10^5	nil.	nil.
Mixed α- and β-isomers	1 : 10^4	1 : 10^4	nil.	nil.
α-7-Aminocholestanol	1 : 10^4	1 : 10^4	nil.	nil.

It will be seen that all the substances showed appreciable antibacterial activity against the Gram-positive organisms, although the activity was somewhat reduced in serum broth. However, there does not seem to be any specific activity connected with the spatial configuration of the basic group in position 7. Some difference might have been expected if the antibacterial potency is in any way connected with the surface activity.

Experimental.

α- *and* β-7-*Aminocholesterol.*—The mixture of isomers was isolated as the hydrochloride exactly as described by Eckhardt (*loc. cit.*), and the free bases obtained by extraction from alkaline solution with freshly redistilled ether. Crystallisation from methyl alcohol–acetone gave a *ca.* 40% yield of the mixed free bases, m. p. 170—185°.

α- *and* β-7-N-*Acetamidocholesterol.*—The mixed 7-amino-bases (2·0 g.) were dissolved in absolute ether (400 c.c.) and a solution of acetic anhydride (6 c.c.) in ether (40 c.c.) added. A crystalline mass separated after a few minutes. It was left at room temperature overnight, then filtered off and washed with absolute ether. The α-form was isolated first by virtue of its low solubility in absolute alcohol. By careful fractionation of the ethyl alcoholic mother liquors obtained after removing most of the relatively insoluble α-form, a fairly complete separation of the two forms was achieved, *viz.* 705 mg. of the α-form and 980 mg. of the β-form, from 2 g. of the original bases. The α-*isomer* formed glistening leaflets after recrystallisation from chloroform–methyl alcohol, m. p. 291—293° (decomp.) unchanged by two further recrystallisations, $[\alpha]_D^{19°}$ −183° (*c*, 0·2 in 1 : 1 chloroform–methyl alcohol) (Found : N, 3·13. Calc. for $C_{29}H_{49}O_2N$: N,

3·16%). The *β-form* was obtained as large regular rectangular prisms after recrystallisation from absolute alcohol, m. p. 277—279° (decomp.) unchanged by two further recrystallisations, $[\alpha]_D^{15°}$ +81° (*c*, 1 in 1 : 1 chloroform–methyl alcohol) (Found : N, 3·27%.) A mixture of the two isomers had m. p. 261—264°.

Attempted Hydrolysis of 7-N-*Acetamidocholesterol.*—(*a*) Treatment of the *N*-acetyl derivative (50 mg.) with 4% methyl alcoholic sodium hydroxide solution, refluxing for 2 hours, yielded the starting material unchanged (35 mg.), m. p. 290—291°.

(*b*) Treatment with 30% methyl alcoholic sodium methoxide for 16 hours in boiling solution gave a small amount of unchanged material. The residue could not be crystallised.

(*c*) Treatment of the *β*-isomer (50 mg.) with methyl alcohol–concentrated hydrochloric acid (1 : 1 mixture), for 1½ hours in boiling solution, gave the unchanged *β*-isomer (20 mg.) after recrystallisation, m. p. 277—279°.

(*d*) Treatment as for (*c*), but boiling for 16 hours. Extraction of the acid solution with ether gave non-basic material (35 mg.) which contained no nitrogen. Ammonium chloride had sublimed on the condenser, hence this treatment apparently removed the amino group completely. The acid-soluble fraction, on being made alkaline and extracted with ether, yielded only 4 mg. of basic material.

(*e*) Treatment with 4% methyl alcoholic hydrogen chloride in a sealed tube at 80° overnight, followed by 6 hours' heating at 130°, gave unchanged starting material.

(*f*) Treatment as in (*e*), leaving at 15° for 3 days, also effected no change.

(*g*) Treatment with 10% methyl alcoholic hydrochloric acid again yielded unchanged material.

In view of these results attempts at hydrolysis were abandoned.

Attempted Separation of the Free Bases on a Column of Alumina.—The mixed free base (250 mg.) was adsorbed on a small tower of alumina in a small volume of benzene. The tower was eluted successively with light petroleum (b. p. 40—60°) (*ca.* 200 c.c.), and then with benzene, *ca.* 50 c.c. of eluate being collected each time. After *ca.* 200 c.c. of benzene had passed through, the free base was obtained from the eluate in three successive fractions. The first of these, on crystallisation from methyl alcohol–acetone, yielded the *β*-isomer as cubes, m. p. 193—195°; the other two fractions gave mixtures of *α*- and *β*-forms.

Fractional Crystallisation.—The mixed 7-amino-isomers (7 g.) were dissolved in methyl alcohol (90 c.c.), and acetone (50 c.c.) was added. After seeding with a crystal of the *β*-form and leaving for 30 minutes, a crop of cubes (*β*-form) was obtained (2·08 g.), m. p. 189—192° rising to 198—199° after two more recrystallisations and unchanged by further crystallisation. Concentration of the filtrate to half the bulk yielded a mixture of cubes and diamonds (2·5 g.). The mother liquors on standing, after seeding with a crystal of the *α*-form, gave the pure *α*-isomer as diamond-shaped prisms (2·46 g.), m. p. 183—185° unchanged by further recrystallisation from methyl alcohol–acetone. The *α*-form appears to exist in two crystalline modifications; when the diamond-shaped prisms (m. p. 183°) were recrystallised from methyl alcohol alone, hair-like needles came down, m. p. 140—142°, and were much more soluble in acetone than the prisms. Recrystallisation of these needles from acetone again gave the diamonds, m. p. 183—185°.

α-7-Aminocholesterol had m. p. 183—185°, $[\alpha]_D^{20°}$ −327° (*c*, 0·74 in chloroform) (Found : N, 3·42. $C_{27}H_{47}ON$ requires N, 3·49%). Second form : needles, m. p. 140—142°, $[\alpha]_D^{20°}$ −80° (*c*, 0·94 in 1 : 1 chloroform–methyl alcohol).

The *α*-amino-isomer (37 mg.), dissolved in absolute ether (10 c.c.), was treated with acetic anhydride (0·12 c.c.) and left overnight at 10°. This yielded *α*-7-*N*-acetamidocholesterol (33 mg.), m. p. 291—293°, giving no depression with that isolated from the original mixture of *N*-acetyl derivatives, $[\alpha]_D^{20°}$ −194° (*c*, 0·5 in 1 : 1 chloroform–methyl alcohol).

β-7-Aminocholesterol had m. p. 198—199°, $[\alpha]_D^{20°}$ +181° (*c*, 0·72 in chloroform) (Found : N, 3·44%).

The *β*-7-amino-isomer (40·0 mg.) was acetylated as described for the *α*-form. *β-N*-Acetamidocholesterol was obtained (30·0 mg.), m. p. 277—279° (decomp.), $[\alpha]_D^{18°}$ +85° (*c*, 0·56 in 1 : 1 chloroform–methyl alcohol).

From the final mother liquor of the 7-aminocholesterol isomers a crystalline, non-nitrogenous material was isolated as clusters of fine needles, m. p. 175—176° after two recrystallisations from acetone. It gave a considerable depression of m. p. both with the 7-amino-isomers and with the original oxime. The analysis was correct for a 7-hydroxycholesterol (Found : C, 80·48; H, 11·49. Calc. for $C_{27}H_{46}O_2$: C, 80·59; H, 11·53%). This could presumably only arise by reduction and simultaneous hydrolysis of 7-ketocholesteryl acetate which might have been present in a small quantity in the oxime used.

α-7-Aminocholestanol.—*α*-7-Aminocholesterol (830 mg.), dissolved in glacial acetic acid (20 c.c.), was hydrogenated in the presence of a platinum black catalyst (0·3 g.) at atmospheric pressure. The theoretical amount of hydrogen (2 atoms = 44 c.c.) was taken up in four minutes. The filtrate was concentrated under reduced pressure to small bulk, neutralised with sodium carbonate solution, made alkaline with sodium hydroxide, and extracted three times with ether. The ethereal extracts, after washing with dilute alkali and drying (Na_2SO_4), were evaporated to dryness (weight 820 mg.). The residue was readily soluble in ethyl and methyl alcohols and in light petroleum. It was crystallised by dissolving in boiling 80% aqueous ethyl alcohol; on cooling flocks of needles appeared, m. p. 84—86° to an opaque liquid. Yield of pure material, 645 mg. Further recrystallisation raised the m. p. to 87—89° (sintered at 84°), $[\alpha]_D^{16°}$ −143° (*c*, 1·1 in absolute alcohol). Addition of ethereal hydrogen chloride to a solution of this base (400 mg.) in absolute ether precipitated the *hydrochloride* as a dry white powder (420 mg.) (Found : N, 3·22. $C_{27}H_{49}ON,HCl$ requires N, 3·18%).

β-7-Aminocholestanol.—Reduction of the *β*-isomer proceeded exactly as described for the *α*-form. The product, however, has not yet been obtained crystalline.

The authors thank Professor W. N. Haworth, F.R.S., Dr. M. Stacey, and Mr. F. A. Robinson for their interest in this work and the following two investigations. They are grateful to Dr. J. Ungar of Glaxo Laboratories Ltd. for carrying out the bacteriostatic tests and to Miss H. King for all microanalyses.

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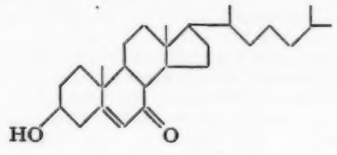
104. *Aminosteroids. Part II. Preparation of* 3 : 7-*Diketocholestene.*

By Jean Barnett, Brenda E. Ryman, and F. Smith.

3 : 7-*Diketocholestene* has been prepared from 7-ketocholesterol. An improved method for the preparation of the latter is also described. The diketone appears to exist only in the enolic form.

The preparation of 3 : 7-*diketocholestene* was undertaken to complete a series of diketosteroids which were required as intermediates for the preparation of diaminosteroids.

The starting material, 7-ketocholesterol (I), was prepared by Mauthner and Suida (*Monatsh.*, 1896, **17**, 579) and by Windaus (*Ber.*, 1915, **48**, 854) by hydrolysis of the acetate with boiling alcoholic potash; however this method in our hands always yielded considerable amounts of 7-ketocholestadiene (II). We have therefore made use of milder conditions, *viz.*, very dilute aqueous-alcoholic potassium carbonate solution, shaking at room temperature until hydrolysis is complete. In this way a quantitative yield of 7-ketocholesterol was obtained.



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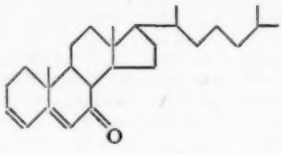

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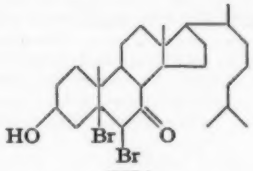

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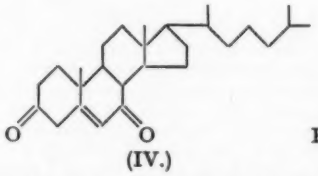

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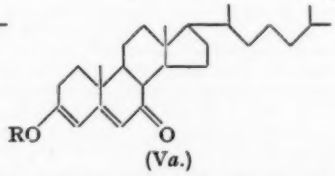
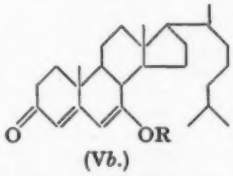
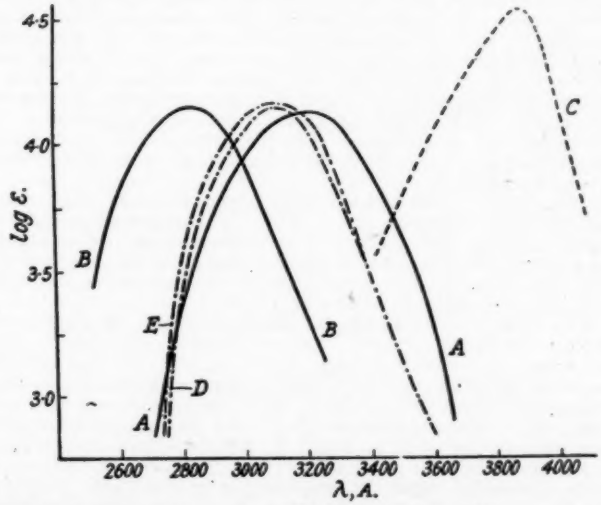


(V*a*.)



(V*b*.)

It was stated by Mauthner and Suida (*loc. cit.*) that 7-ketocholesterol did not absorb bromine. However, it was found that addition of two atoms of bromine to the ketone in carbon disulphide solution at room temperature



A. { *Enol of* 3 : 7-*diketocholestene in ethyl alcohol* (2·4 *mg.*-%).
{ *Enol acetate after making alkaline followed by reacidification* (3 *mg.*-%).
B. *Enol acetate in neutral* EtOH (3 *mg.*-%).
C. { *Enol of* 3 : 7-*diketocholestene in alkaline* EtOH (*ca.* 5 × 10^{-3} N; 0·48 *mg.*-%).
{ *Enol acetate in alkaline solution* (0·76 *mg.*-%).
D. *Methyl ether of enol in neutral or alkaline* EtOH (3 *mg.*-%).
E. *Ethyl ether of enol in neutral or alkaline* EtOH (3 *mg.*-%).

readily yielded the *dibromide* (III), m. p. 124—125°. The latter on oxidation with chromic acid and subsequent debromination yielded 3 : 7-diketocholestene, m. p. 185—186°, which dissolved readily in sodium hydroxide solution and on re-acidification yielded the same product. No evidence was obtained that it existed in two forms; the stable form would appear, from all available evidence, to be the enolic form. It yielded a monoacetate and a monomethyl ether readily. The absorption curves of these substances are shown in the figure. That of the enol itself [(A), fig.] shows a maximum at λ 3220 A. and is practically identical with that of its *methyl ether* [(D), fig.], thus affording evidence of its enolic structure. If it were a diketone (IV) rather than an enol (V*a* or V*b*), it would be expected to show absorption at about λ 2400 A. Addition of alkali to the enol caused a displacement of the band to λ 3900 A. The enol acetate [(B), fig.] shows a maximum absorption at λ 2840 A.; in alkali the band shifts to λ 3900 A. but on acidification the maximum appears at λ 3200 A. (identical with that of the enol), thus indicating extreme lability of the enolic acetyl group. The enol may have either of the structures shown in formulæ (V*a*) and (V*b*) (R = H). There is no evidence at present which favours one rather than the other. A *dioxime* was obtained without any difficulty.

EXPERIMENTAL.

7-Ketocholesterol (I.).—7-Ketocholesteryl acetate (50 g.) was suspended in methyl alcohol (5 l.) and a solution of potassium carbonate (16 g.) in water (300 c.c.) added. The mixture was shaken mechanically at 20° for 20 hours. The clear yellow liquid was diluted with water, concentrated under reduced pressure at 20° to small bulk, and extracted four times with ether. After having been washed three times with water the extracts were dried (Na_2SO_4) and the solvent removed by distillation. The residue was crystallised from hot methyl alcohol by addition of water until almost cloudy, m. p. (after drying in a vacuum at 50°) 159—161° (28 g.). A second crop of 14 g., m. p. 160—161°, was obtained by concentration of the mother liquors. Recrystallisation from ether–light petroleum did not change the m. p.

7-Ketocholestadiene (II).—7-Ketocholesteryl acetate (50 g.) dissolved in boiling methyl alcohol (300 c.c.) was treated with 5% methyl alcoholic sodium hydroxide (250 c.c.). The dark brown solution was refluxed for 30 minutes. After dilution with water, the cooled solution was neutralised with carbon dioxide and evaporated under reduced pressure to half bulk. After extraction with ether, the product was recrystallised from methyl alcohol, and then had m. p. 110—112°. It gave no depression with 7-ketocholestadiene, m. p. 112°. The absorption curve of this compound is shown in the figure.

5 : 6-Dibromo-7-ketocholesterol (III).—7-Ketocholesterol (42 g.) was dissolved in warm freshly redistilled carbon disulphide (300 c.c.). The solution was cooled to 20°, and a solution of bromine (9 c.c.) in carbon disulphide (20 c.c.) was added. The solution became warm after standing for a few minutes and was kept cool with running water. After 10 minutes at 20°, it was evaporated under reduced pressure in a bath at 30° to a thick syrup. This was taken up in ether (100 c.c.) and ethyl alcohol (200 c.c.) added. *5 : 6-Dibromo-7-ketocholesterol* crystallised at once as flocks of needles (21 g.), m. p. 123—124° (decomp.). Careful concentration of the mother liquor yielded a further crop (4·5 g.) but the filtrate decomposed with evolution of bromine when evaporated further under reduced pressure at 40°. Recrystallisation of the first crop from ether–absolute alcohol gave glistening needles, m. p. 124—125° (decomp.), $[\alpha]_D^{17°}$ − 5·6° (*c*, 0·88 in chloroform) (Found: C, 57·65, 57·73; H, 8·04, 8·27. $C_{27}H_{44}O_2Br_2$ requires C, 57·84; H, 7·91%). Dibromo-7-ketocholesterol is soluble in ether and carbon disulphide, but practically insoluble in alcohol and light petroleum.

3 : 7-Diketocholestene, Enolic Form [(V*a*) or (V*b*), R = H].—*5 : 6*-Dibromo-7-ketocholesterol (22 g.), dissolved in benzene (220 c.c.), was shaken for 5 hours with a solution of chromic oxide (14·3 g.) in water (66 c.c.) and glacial acetic acid (143 c.c., distilled over chromic oxide). The benzene layer was separated, washed once with water, and then treated with glacial acetic acid (110 ml.) and zinc wool (7·7 g.). Most of the benzene was distilled off (water-bath); the residue was refluxed for one hour (bath temperature 115°). The cooled liquid was filtered through glass wool and the filtrate extracted three times with ether. The ethereal extracts were washed twice with water, then three times with dilute sodium hydroxide solution. The combined alkaline extracts were acidified with dilute sulphuric acid and the yellowish precipitate filtered off. This solid was extracted with ether (2 l.). After the ethereal solution had been dried and the solvent evaporated, the residue was crystallised from ether–light petroleum, yielding glistening rectangular leaflets, m. p. 185—186° (5·8 g.). From the mother liquor a further amount (4·8 g.) was obtained, m. p. 184—185°. The m. p. was unchanged by a further recrystallisation either from methyl alcohol or from ether–light petroleum, $[\alpha]_D^{16·5°}$ − 53° (*c*, 1·0 in chloroform) (Found: C, 81·37, 81·56; H, 10·84, 10·95. $C_{27}H_{42}O_2$ requires C, 81·34; H, 10·63%). The absorption curve for this *substance* is shown in the figure. The diketone is soluble in ethyl and methyl alcohols, acetone, and benzene, difficultly soluble in ether, and insoluble in light petroleum. The crystals darken, after exposure to light for several weeks, to a golden brown colour.

Methyl Ether [(V*a*) or (V*b*), R = Me].—*3 : 7*-Diketocholestene (enol form, 200 mg.) was refluxed for one hour with methyl alcohol (20 c.c.) and concentrated sulphuric acid (2 c.c.). The cooled solution, after dilution with ether, was extracted three times with water, then once with dilute sodium hydroxide solution, to remove any traces of unchanged enol. After washing once more with water, the ethereal solution was dried (Na_2SO_4) and evaporated to dryness. The residue (150 mg.) was recrystallised twice from methyl alcohol yielding the *methyl ether*, m. p. 136—137° (50 mg.) (Found: C, 81·56; H, 11·02. $C_{28}H_{44}O_2$ requires C, 81·55; H, 10·76%).

Enol Acetate [(V*a*) or (V*b*), R = COMe].—*3 : 7*-Diketocholestene (enol form, 50 mg.) was kept with absolute pyridine (1 c.c.) and acetic anhydride (0·5 c.c.) at 15° for 15 hours. The red solution, after dilution with iced ether, was extracted twice with ether, and the extract was washed with ice-cold dilute hydrochloric acid and then with water. The dried ethereal extract was concentrated under reduced pressure and the residue crystallised from methyl alcohol, in which it was very soluble, at 0°. The enol acetate obtained had m. p. 106—108°. Its absorption curve is shown in the figure.

3 : 7-Diketocholestene Dioxime.—*3 : 7*-Diketocholestene (5 g.) was dissolved in hot ethyl alcohol (150 c.c.) and treated with a solution of hydroxylamine [prepared by dissolving hydroxylamine hydrochloride (4 g.) and fused sodium acetate (6 g.) in water (5 c.c.), adding alcohol (20 c.c.) and filtering of the precipitated sodium chloride]. This solution was refluxed for 5 hours. The crystals which came out on cooling were filtered off, washed with 80% aqueous alcohol, then with absolute alcohol, and finally with ether. Yield 3·0 g., m. p. 229—230° (decomp.). A further crop (1·2 g.), obtained by concentration of the mother liquor, had m. p. 229—230°. The *dioxime* was insoluble in ether and benzene, only very slightly soluble in boiling alcohol, and rather more soluble in boiling dioxan. Recrystallisation from either boiling ethyl alcohol or dioxan gave needles, m. p. 229—230° (decomp.) (Found: C, 75·68, 75·46; H, 10·23, 10·37. $C_{27}H_{44}O_2N_2$ requires C, 75·70; H, 10·36%).

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105. *Aminosteroids. Part III. Some Mono- and Di-aminosteroids.*

BY JEAN BARNETT, BRENDA E. RYMAN, and F. SMITH.

Various mono- and di-aminosteroids have been prepared by reduction of the oximes of the corresponding mono- and di-ketosteroids. Examination of their properties as antibacterial agents *in vitro* against Gram-positive organisms showed a marked and similar activity in all compounds studied. Only the diaminosteroids had any appreciable bacteriostatic activity against Gram-negative organisms.

IN continuation of the study of aminosteroids (Part I, Barnett, Ryman, and Smith, this vol., p. 524) various mono- and di-aminosteroids have been made by reduction of the corresponding mono- and di-oximes. Table I shows the ketones which were used as starting products, together with their oximes, with reference to their method of preparation when they were already known. No difficulty was experienced in the synthesis of any

of the oximes except that from 6 : 7-diketocholestanyl acetate; presumably steric hindrance retarded its formation, for complete oximation was effected only after refluxing the components for 48 hours.

TABLE I.

Ketone.	M. p.	Reference.	Oxime.	Reference.
6-Ketocholestanyl acetate	122—124°	Heilbron *et al.*, *J.*, 1938, 104.	201—202°	—
Cholestenone	79—80	*Helv. Chim. Acta*, 1934, **17**, 1413.	152	*Ber.*, 1904, **37**, 3101.
7-Ketocholesteryl acetate	153—154	Windaus, Lettré, and Schenk, *Annalen*, 1935, **520**, 98.	184—185	Eckhardt, *Ber.*, 1938, **71**, 467.
3 : 7-Diketocholestene	184—185	Barnett, Ryman, and Smith, Part II, this vol., p. 526.	229—230	Barnett, Ryman, and Smith, *loc. cit.*
3 : 6-Diketocholestane	169—170	Windaus, *Ber.*, 1903, **36**, 3755.	205—210	Windaus, *loc. cit.*
6 : 7-Diketocholestanol	152—153	—	245—247	—

Biological Results.—Monoaminosteroids were prepared as their hydrochlorides for testing; diaminosteroids were in the form of their dilactates, since their dihydrochlorides were too insoluble to be of use. Dilutions of from $1 : 10^3$ to $1 : (5 \times 10^5)$ were tested *in vitro* in synthetic media, glucose broth, and (a few) in serum broth, against *Streptococcus hæmolyticus*, *Staphylococcus aureus*, *B. coli*, and *Ps. pyocyanea*. Results are shown in Table II. Results with 7-aminocholesterol are included for the comparison.

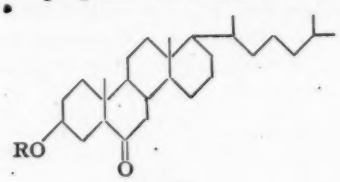
TABLE II.

Limiting dilution giving complete inhibition of growth.

Synthetic medium.	*Strep. hæm.*	*Staph. aur.*	*B. coli.*	*Ps. pyoc.*
3-Aminocholestene [1]	$1 : 10^4$	$1 : 10^4$	nil.	nil.
3-Aminocholestane [2]	$1 : 10^5$	$1 : 5 \times 10^4$	$1 : 10^3$	nil.
6-Aminocholestanol	$1 : 10^5$	$< 1 : 10^5$	$< 1 : 10^3$	$< 1 : 10^3$
7-Aminocholesterol (β)[3]	$1 : (5 \times 10^5)$	$1 : (5 \times 10^5)$	nil.	nil.
7-Dimethylaminocholesterol [4]		Not tested.		
3 : 7-Diaminocholestene	$1 : 10^5$	$1 : (5 \times 10^5)$	$1 : 10^4$	$1 : 10^4$
3 : 6-Diaminocholestane	$1 : 10^5$	$1 : (5 \times 10^5)$	$1 : 10^4$	nil.
6 : 7-Diaminocholestanol	$1 : 10^5$	$1 : 10^5$	$1 : (5 \times 10^3)$	$1 : 10^3$
Glucose broth.				
3-Aminocholestene	$1 : (5 \times 10^3)$	$1 : (5 \times 10^3)$	nil.	nil.
3-Aminocholestane	$1 : 10^4$	$1 : (5 \times 10^3)$		
6-Aminocholestanol	$< 1 : 10^5$	$< 1 : 10^5$	$1 : 10^4$	$1 : (5 \times 10^3)$
7-Aminocholesterol	$1 : (5 \times 10^3)$	$1 : 10^5$	nil.	nil.
7-Dimethylaminocholesterol		Not tested.		
3 : 7-Diaminocholestene	$1 : 10^5$	$1 : (5 \times 10^4)$	$1 : 10^4$	$1 : (5 \times 10^3)$
3 : 6-Diaminocholestane	$1 : 10^5$	$1 : (5 \times 10^5)$	$1 : 10^4$	$1 : (5 \times 10^3)$
6 : 7-Diaminocholestanol	$1 : 10^5$	$1 : 10^5$	$1 : 10^3$	$1 : 10^3$
Serum broth.				
3-Aminocholestene	$1 : (5 \times 10^3)$	$1 : (5 \times 10^3)$	nil.	nil.
3 : 7-Diaminocholestene	$1 : (5 \times 10^4)$	$1 : (5 \times 10^3)$	$1 : (5 \times 10^3)$	$1 : 10^3$

[1] Windaus and Adamla, *Ber.*, 1911, **44**, 3051. [2] Diels and Stamm, *Ber.*, 1912, **45**, 2232. [3] Part I, *loc. cit.* [4] Eckhardt, *Ber.*, 1938, **71**, 467.

It will be seen from Table II that all the aminosteroids so far tested are highly active *in vitro* against *Streptococci* and *Staphylococci*; on the whole the diaminosteroids appear to possess a consistently higher antibacterial potency than the monoaminosteroids. Moreover, the group of diamino compounds shows considerable bacteriostatic activity against the Gram-negative organisms tested. *In vivo* tests on some of these bases are in progress. It is hoped to continue the investigation to cover triaminosteroids.



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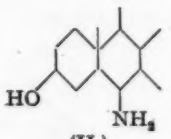

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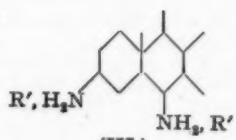

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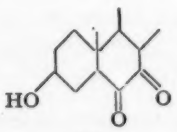

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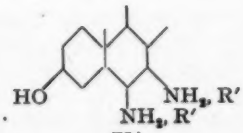

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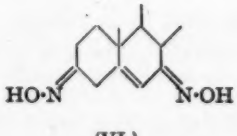

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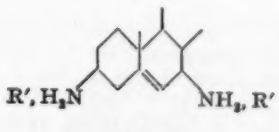

(VII.)

R = Ac. R′ = Lactic acid.

Experimental.

6-Ketocholestanyl Acetate (I, R = Ac).—This was prepared by the method of Heilbron *et al.* (*J.*, 1938, 104). The purity of the nitration product was found to depend very much on the strength of the fuming nitric acid used, and on the efficiency of the stirring.

Oxime of 6-Ketocholestanyl Acetate.—6-Ketocholestanyl acetate (200 mg.) was treated with hydroxylamine hydrochloride and sodium acetate, refluxing in alcoholic solution for 8 hours. On cooling, the oxime settled out as glistening plates. Recrystallisation from aqueous alcohol gave the *oxime* (150 mg.), m. p. 201—202° (Found: C, 75·95; H, 10·72; N, 3·31. $C_{29}H_{49}O_3N$ requires C, 75·82; H, 10·68; N, 3·05%).

6-Aminocholestanol hydrochloride (II) was obtained by reduction of the oxime as described previously (Found: N, 3·18. $C_{27}H_{49}ON,HCl$ requires N, 3·20%). It was soluble in alcohol and insoluble in water.

3 : 6-Diketocholestane.—This was prepared by oxidation of 6-ketocholestanol as described by Windaus (*loc. cit.*). The dioxime, prepared as already described, had m. p. 205—210° (decomp.).

3 : 6-Diaminocholestane dilactate (III) was prepared by reduction of the dioxime in the usual manner (Found: N, 4·31. $C_{27}H_{50}N_2,2C_3H_6O_3$ requires N, 4·79%). It was readily soluble in alcohol and water.

6 : 7-Diketocholestanol (IV).—The acetate was prepared from 7-bromo-6-ketocholestanyl acetate by treatment with silver nitrate and pyridine (Heilbron *et al.*, *J.*, 1937, 803); it had m. p. 156—157°.

6 : 7-Diketocholestanyl acetate (500 mg.) was dissolved in warm 2% methyl alcoholic sodium hydroxide solution (10 c.c.) and refluxed for 15 minutes. Water was added, then dilute sulphuric acid until the solution was acid. After extracting the product three times with ether and washing well with water, evaporation of the ethereal extracts yielded a crystalline product which was recrystallised from methyl alcohol by addition of water giving *6 : 7-diketocholestanol* as needles (400 mg.), m. p. 149—151°. Repeated recrystallisation raised the m. p. to 152—153°. The compound gave a deep green colour with alcoholic ferric chloride (Found: C, 75·46; H, 10·60. $C_{27}H_{44}O_3$ requires C, 75·0; H, 10·8%).

Dioxime of 6 : 7-Diketocholestanyl Acetate.—Preparation of this oxime gave some difficulty; treatment for three hours or eight hours with hydroxylamine gave unchanged diketone; the following method was finally used: 6 : 7-diketocholestanyl acetate (200 mg.) was refluxed for 48 hours in alcoholic solution with four times the theoretical amount of hydroxylamine. The end of the reaction could be ascertained when no crystalline material separated on cooling, since the oxime was extremely soluble in alcohol. Addition of water to the alcoholic solution caused the separation of the *dioxime* as fine white needles, m. p. 242—244° (110 mg.). A further crop was obtained on concentration of the filtrate (80 mg.; m. p. 240—241°). Recrystallisation from aqueous methyl alcohol gave fine feathery needles, m. p. 245—247° (Found: C, 71·97, 71·90; H, 10·01, 9·96; N, 5·59. $C_{29}H_{48}O_4N_2$ requires C, 71·32; H, 9·91; N, 5·73%).

6 : 7-Diaminocholestanol Dilactate (V).—This was prepared in the usual way by reduction of the dioxime (880 mg.), yielding the *dilactate* as a white deliquescent powder (603 mg.) (Found: N, 4·78. $C_{27}H_{50}ON_2,2C_3H_6O_3$ requires N, 4·7%). It was soluble in water and alcohol but insoluble in ether.

3 : 7-Diaminocholestene (VII).—The steroid base was obtained by reduction of 3 : 7-diketocholestene dioxime (VI) (Part II, *loc. cit.*) with sodium in ethyl alcoholic solution. 4 G. of dioxime yielded 3·9 g. of the diamino-dihydrochloride. As the dihydrochloride was insoluble in alcohol as well as in water, and would therefore be useless for testing, it was transformed *via* the free base (which was not isolated since it would be a mixture of four possible isomers) into the dilactate by addition of two mols. of lactic acid in ethereal solution to the solution of the base in dry ether. The dilactate was precipitated as a yellowish powder, which was readily soluble in cold alcohol and soluble in water on slight warming, but which could not be recrystallised.

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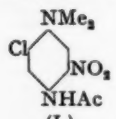
106. p-*Aminodimethylaniline. Part III. The Orientation of Groups in the Disubstituted Molecule.*

By Ernest E. Ayling, John H. Gorvin, and Leonard E. Hinkel.

The study of the influence of nuclear substituents on the coupling power of diazotised *p*-aminodimethylaniline (compare Parts I and II, *J.*, 1941, 613; 1942, 755) required the preparation of derivatives of the base having chloro- or nitro-groups in the *o*- and *m*-positions to the dimethylamino-group. 2-Chloro-4-acetamidodimethylaniline yields the 5-nitro-derivative by nitration in sulphuric acid. In the chlorination of 3-nitro-4-acetamidodimethylaniline and in the nitration of 3-chloro-4-acetamidodimethylaniline substitution occurs in the 2- instead of the 6-position.

As a result of the exceptionally strong *op*-directing activity of the dimethylamino-group, substituents normally enter *p*-acetamidodimethylaniline in one or both of the *o*-positions (compare Part II). A single nitro-group can, however, be introduced into the *m*-position by nitration in concentrated sulphuric acid (Hodgson and Crook, *J.*, 1932, 2976), the point of attack being here determined by the acetamido-group. In a similar manner,



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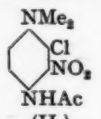

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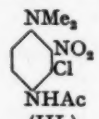

(III.)

2-chloro-5-nitro-4-acetamidodimethylaniline (I) was obtained by the nitration of 2-chloro-4-acetamidodimethylaniline (compare Part II) in concentrated sulphuric acid; its structure was verified by deacetylation and deamination of the resulting *base* to 2-chloro-5-nitrodimethylaniline (compare van Duin, *Rec. Trav. chim.*, 1932, 51, 878).

Since in the nitration of 3-nitro-4-acetamidodimethylaniline the second nitro-group had been reported to enter the 6-position to give the compound usually termed 2 : 5-dinitro-4-acetamidodimethylaniline (Hodgson and Crook, *J.*, 1934, 873), it was expected that chlorination would yield the red 2-chloro-5-nitro-compound (I).

Instead, however, the product consisted entirely of a pale yellow substance considered to be 2-*chloro*-3-*nitro*-4-*acetamidodimethylaniline* (II), since the compound obtained on deacetylation and deamination of the resulting *base* was identical with 2-*chloro*-3-*nitrodimethylaniline* prepared by methylation of 2-chloro-3-nitroaniline (compare Wallagh and Wibaut, *Rec. Trav. chim.*, **1936**, **55**, 1074). Similarly, the nitration of 3-chloro-4-acetamidodimethylaniline with nitrous acid, with a mixture of nitric acid and hydrochloric acid (compare Part II), or with nitric acid in concentrated sulphuric acid, gave only 3-*chloro*-2-*nitro*-4-*acetamidodimethylaniline* (III); this compound, by hydrolysis to the free *base* and subsequent deamination, was converted into 3-chloro-2-nitrodimethylaniline (compare Hodgson and Nicholson, *J.*, **1941**, 766).

Substitution in the 2- rather than in the 6-position of the 3-chloro-compound is readily accounted for by the mechanism suggested by Hodgson and Nicholson (*loc. cit.*) for the comparable case of nitration of the 3-halogenodimethylanilines which gives the 2- as well as the 4-nitro-derivatives. Since, however, the 4-position is now occupied, the most strongly activated point in 3-chloro-4-acetamidodimethylaniline will be the 2-position, and the resulting yield of 2-nitro-derivative is high. Similar considerations apply to the chlorination of 3-nitro-4-acetamidodimethylaniline, especially as it has now been found possible to isolate some 2-chloro-3-nitrodimethylaniline from the product of chlorination of 3-nitrodimethylaniline.

It appears that another factor enters into the nitration of the 3-nitro-derivatives. Forster and Coulson (*J.*, **1922**, **121**, 1988) commented on the absence of 2 : 3-dinitrodimethylaniline from the nitration products of 3-nitrodimethylaniline (compare also Macmillan and Reade, *J.*, **1929**, 2865; Hodgson and Smith, *J.*, **1931**, 1508). Similarly, Hodgson and Crook (*loc. cit.*) recorded 2 : 5-dinitro-4-acetamidodimethylaniline (*i.e.*, 3 : 6-dinitro-) as the only nitration product of 3-nitro-4-acetamidodimethylaniline. These observations rested on the conclusion of Forster and Coulson (*loc. cit.*) that the red dinitrodimethylaniline, m. p. 112°, of van Romburgh (*Rec. Trav. chim.*, **1887**, **6**, 253; compare also Vorländer and Siebert, *Ber.*, **1919**, **52**, 297, and Swann, *J.*, **1920**, **117**, 3) was in fact the 2 : 5-compound; this has now been confirmed by its preparation from 2 : 5-dinitroaniline by methylation.

The preferential formation of the 2 : 5-dinitro-derivative would seem to be a steric effect; the amount of space available in the 2-position, when the 3-position is occupied by a nitro-group, is not great, particularly as the mesomerism of the dimethylamino-group requires that the *N*-methyl groups should tend to lie in the plane of the benzene ring (Birtles and Hampson, *J.*, **1937**, 10). Thus, although the space in the 2-position may be quite adequate to receive a chloro-group, the larger nitro-group is diverted into the 6-position, even though this may be less strongly activated. Nevertheless, there does appear to be some tendency towards 2-substitution, for the nitration of *p*-acetamidodimethylaniline in sulphuric acid and the nitration of 3-nitro-4-acetamidodimethylaniline with nitrous acid or with a mixture of nitric acid and hydrochloric acid give, in addition to the deep red 2 : 5-dinitro-compound of Hodgson and Crook (*loc. cit.*), a smaller amount of an orange-yellow *dinitro*-derivative which, by exclusion, must be the 2 : 3-compound. Like certain other 2-nitro-compounds of this type (compare Part II), it cannot be deacetylated without decomposition, and it has therefore not been possible to verify its structure by degradation.

Experimental.

2-*Chloro*-5-*nitro*-4-*acetamidodimethylaniline* (I).—To a solution of 2-chloro-4-acetamidodimethylaniline (2·12 g.) (cf. Part II) in concentrated sulphuric acid (8 c.c.) was added a mixture of nitric acid (1·4 c.c., *d* 1·5) and sulphuric acid (6 c.c.) at 0°. After an hour the mixture had become deep yellow; it was poured on to ice, filtered to remove traces of nitrosoamine, and neutralised with ammonia. 2-*Chloro*-5-*nitro*-4-*acetamidodimethylaniline* (1·34 g., 52%) was precipitated, and crystallised from alcohol as a coppery-red felted mass of fine needles, m. p. 124° (Found : Cl, 13·9. $C_{10}H_{12}O_3N_3Cl$ requires Cl, 13·8%). The compound was soluble in 10% sodium hydroxide solution and could be recovered unchanged by acidification and neutralisation with ammonia.

2-*Chloro*-5-*nitro*-4-*aminodimethylaniline*.—The acetyl derivative was hydrolysed by boiling for 3 minutes with 40% sulphuric acid. On cooling and basifying, 2-*chloro*-5-*nitro*-4-*aminodimethylaniline* separated; it crystallised from ligroin (b. p. 80—100°) in dark red square plates, m. p. 92—93° (Found : Cl, 16·5. $C_8H_{10}O_2N_3Cl$ requires Cl, 16·5%).

A solution of the base (1 g.) in 40% sulphuric acid (5 c.c.) was diazotised with sodium nitrite and refluxed with alcohol (50 c.c.) for 30 minutes. On concentration of the solution and addition of ammonia, 2-chloro-5-nitrodimethylaniline was obtained; it crystallised from alcohol, after treatment with charcoal, in bright yellow prismatic rods, m. p. 64—65°, and was identical with an authentic specimen prepared in 90% yield from *o*-chlorodimethylaniline by the method of van Duin (*loc. cit.*).

2-*Chloro*-3-*nitro*-4-*acetamidodimethylaniline* (II).—3-Nitro-4-acetamidodimethylaniline was prepared in 65% yield by the method of Hodgson and Crook (*J.*, **1932**, 2976). After treatment of its alcoholic solution with charcoal it crystallised in deep red prisms, m. p. 124° (Found : N, 18·5. Calc. : N, 18·8%). (Hodgson and Crook record m. p. 116°.) Chlorine was passed into a solution of this compound (2·23 g.) in dry chloroform at room temperature. The colourless hydrochloride which separated was washed with chloroform and its aqueous solution basified; 2-*chloro*-3-*nitro*-4-*acetamidodimethylaniline* (2·05 g., 80%) separated and crystallised from aqueous methanol in pale yellow leaflets, m. p. 159—160° (Found : Cl, 13·8. $C_{10}H_{12}O_3N_3Cl$ requires Cl, 13·8%). This compound was not affected by further treatment with chlorine in chloroform solution. It did not react with nitrous acid, but gave a nitrosoamine derivative on dissolving in nitric acid (*d* 1·4).

2-*Chloro*-3-*nitro*-4-*aminodimethylaniline*.—A solution of the foregoing acetyl derivative in 40% sulphuric acid was raised to the boiling point. On cooling and basifying 2-*chloro*-3-*nitro*-4-*aminodimethylaniline* separated. The base was very soluble in most organic solvents, but crystallised from ligroin (b. p. 80—100°) in yellowish-red needles, m. p. 57·5° (Found : Cl, 16·4. $C_8H_{10}O_2N_3Cl$ requires Cl, 16·5%).

2-*Chloro*-3-*nitrodimethylaniline*.—(*a*) A solution of 2-chloro-3-nitro-4-aminodimethylaniline (1 g.) in hydrochloric acid (5 c.c., *d* 1·2) and water (5 c.c.) was diazotised with sodium nitrite (0·32 g.) in water (5 c.c.). The solution was refluxed with alcohol (50 c.c.) for 30 minutes, made alkaline and steam-distilled. 2-*Chloro*-3-*nitrodimethylaniline* passed over very readily and was recovered by extraction with ether. Crystallisation from aqueous alcohol gave golden-yellow leaflets or long flattened needles (0·75 g., 80%), m. p. 41°, having a faint but characteristic odour (Found : Cl, 17·7. $C_8H_9O_2N_2Cl$

requires Cl, 17·7%). The substance was very soluble in light petroleum. It was unaffected by boiling with aqueous sodium hydroxide.

(*b*) *o*-Chloronitrobenzene (100 g.) was nitrated by the procedure of Ostromisslensky (*J. pr. Chem.*, 1908, **78**, 261), and a large amount of crystalline 1-chloro-2 : 4-dinitrobenzene was removed from the ethereal solution of the product. The residual oil (14·5 g.), consisting mainly of the two isomeric dinitro-compounds, was treated with ethyl acetoacetate and sodium methoxide (Borsche and Rantscheff, *Annalen*, 1911, **379**, 152) in order to remove the remainder of the 1-chloro-2 : 4-dinitrobenzene. The unreacted part of the oil was dissolved in benzene and passed through a column of alumina; on removal of the benzene, 2-chloro-1 : 3-dinitrobenzene (3·1 g., 2%) was obtained, which crystallised from alcohol in yellow needles, m. p. 88°. This was reduced to 2-chloro-3-nitroaniline by the method of Wallagh and Wibaut (*loc. cit.*), using the calculated amount of 0·1N-titanous chloride solution. The resulting base, which crystallised from aqueous alcohol in fine yellow needles, m. p. 95—96°, was methylated by heating with methyl sulphate for 3 hours at 150—160°. Subsequent steam-distillation of the alkaline solution gave 2-chloro-3-nitrodimethylaniline identical with the compound obtained by the method (*a*) above.

(*c*) To 3-nitrodimethylaniline (1·7 g., 1 mol.) dissolved in carbon tetrachloride (5 c.c.) was added a solution of chlorine (0·82 g., 1 mol.) in the same solvent (10 c.c.); the mixture became warm and an orange-yellow oil separated. The solvent was removed under reduced pressure and the residue made alkaline and steam-distilled, the initial distillate being collected in four small fractions. The first two of these fractions, when extracted with ether, gave oils which, after crystallisation from aqueous alcohol, yielded 2-chloro-3-nitrodimethylaniline identical with that prepared by methods (*a*) and (*b*). The oils obtained from the third and fourth fractions could not be crystallised.

3-Chloro-4-acetamidodimethylaniline.—This compound, which crystallised from aqueous alcohol in needles, m. p. 117—118°, was prepared substantially as described by Fieser and Thompson (*J. Amer. Chem. Soc.*, 1939, **61**, 383). The intermediate 3-chloro-4-aminodimethylaniline (cf. also Bayer and Co., G.P. 197,035; *Chem. Zentr.*, 1908, I, 1507) crystallised from ligroin (b. p. 40—60°) in prisms, m. p. 40—42°. Unlike 2-chloro-4-aminodimethylaniline (Part II) and 3-nitro-4-aminodimethylaniline, the base gave a positive reaction (a violet colour) in Lauth's test for *p*-diamines.

Nitration of 3-Chloro-4-acetamidodimethylaniline.—(*a*) The acetyl derivative (1 g.) dissolved in hydrochloric acid (2 c.c., *d* 1·2) and water (4 c.c.) was treated with sodium nitrite (0·5 g.) in water (3 c.c.) at 0°. After being left overnight the mixture was made alkaline; the precipitated *3-chloro-2-nitro-4-acetamidodimethylaniline* (III) (0·88 g., 75%) crystallised from alcohol in yellowish-red prisms, m. p. 166° (Found : Cl, 13·6. $C_{10}H_{12}O_3N_3Cl$ requires Cl, 13·8%).

(*b*) 3-Chloro-4-acetamidodimethylaniline (1 g.) dissolved in hydrochloric acid (6 c.c., *d* 1·2) was treated with nitric acid (3 c.c., *d* 1·42) at room temperature. An immediate reaction ensued and, after pouring the mixture into water and making alkaline with ammonia, 3-chloro-2-nitro-4-acetamidodimethylaniline was the only compound which could be isolated.

(*c*) The acetyl derivative (1·95 g.) dissolved in concentrated sulphuric acid (8 c.c.) was treated with nitric acid (1·4 c.c., *d* 1·5) in sulphuric acid (6 c.c.) at 0° and kept overnight in the cold. On pouring into ice-water a solid nitrosoamine derivative (0·37 g.) separated. When the filtered solution was basified a precipitate of 3-chloro-2-nitro-4-acetamidodimethylaniline (1·4 g., 62%) was obtained, identical with that prepared by methods (*a*) and (*b*).

3-Chloro-2-nitro-4-aminodimethylaniline.—The foregoing acetyl derivative (1 g.) was boiled for 2 minutes with 40% sulphuric acid (10 c.c.). On addition of ammonia an oil was obtained, which soon solidified. By fractional extraction and crystallisation from ligroin (b. p. 80—100°) the crude reaction product, which contained some tarry matter, gave *3-chloro-2-nitro-4-aminodimethylaniline* in the form of black plates or needles, m. p. 53—54°, appearing deep red by transmitted light (Found : Cl, 16·5. $C_8H_{10}O_2N_3Cl$ requires Cl, 16·5%).

3-Chloro-2-nitrodimethylaniline.—When 3-chloro-2-nitro-4-aminodimethylaniline was deaminated by a procedure similar to that previously described for related bases, the product of steam-distillation crystallised from aqueous alcohol or ligroin to give 3-chloro-2-nitrodimethylaniline in long, bright yellow needles, m. p. 39° (Found : Cl, 17·7. Calc. : Cl, 17·7%). There was no m. p. depression on admixture with an authentic specimen, m. p. 39°, prepared by the method of Hodgson and Nicholson (*loc. cit.*) who, however, record m. p. 36°.

In the authors' experience, the " initial yellow precipitate " (Hodgson and Nicholson, *loc. cit.*) consisted only of 3-chloro-4-nitrodimethylaniline hydrochloride, whereas the 3-chloro-2-nitrodimethylaniline was present in the filtrate, from which it was readily recovered by steam-distillation. Though considerably less volatile in steam than 3-chloro-2-nitrodimethylaniline, the isomeric 3-chloro-4-nitrodimethylaniline cannot accurately be described as " non-volatile."

2 : 5-Dinitrodimethylaniline.—The mixture of dinitroacetanilides resulting from the nitration of *m*-nitroacetanilide was separated by the usual procedure (cf. Welsh, *J. Amer. Chem. Soc.*, 1941, **63**, 3276) and the 2 : 5-compound was deacetylated to give 2 : 5-dinitroaniline, m. p. 137°. The base (0·62 g.) was heated with methyl sulphate (2 c.c.) at 150—160° for 4 hours and the mixture then made almost alkaline. The dark red precipitate was filtered off and boiled with alcohol, decanting from insoluble tarry matter. The alcoholic solution was evaporated to dryness and the residue warmed with acetic anhydride (1 c.c.), excess of this reagent being removed under reduced pressure. The solid residue was dissolved in hydrochloric acid and the solution extracted several times with ether before final neutralisation. The product (0·4 g., m. p. 105°) was crystallised from aqueous alcohol, filtering through charcoal, to give 2 : 5-dinitrodimethylaniline in red needles (0·33 g.), m. p. 114° (earlier authors record m. p. 112°; Hodgson and Crook give m. p. 114°). The m. p. was not depressed by the compound prepared by nitration of dimethylaniline (van Romburgh, *loc. cit.*) and by deamination of 2 : 5-dinitro-4-aminodimethylaniline (Hodgson and Crook, *J.*, 1934, 873).

2 : 3-Dinitro-4-acetamidodimethylaniline.—(*a*) *p*-Acetamidodimethylaniline (16 g.) was nitrated by the method of Hodgson and Crook (*loc. cit.*). The crude reaction product was dissolved in warm alcohol, filtered through charcoal, and allowed to crystallise. A quantity of 2 : 5-dinitro-4-acetamidodimethylaniline separated from the alcoholic solution, and the concentrated filtrate was finally evaporated to dryness and extracted with benzene. The crystals obtained on evaporating the benzene solution were further purified by addition of carbon tetrachloride to their solution in chloroform; crystallisation from alcohol gave a felted mass of orange-yellow needles, m. p. 171·5—172·5° (Found : C, 44·9; H, 4·5; N, 20·2. $C_{10}H_{12}O_5N_4$ requires C, 44·8; H, 4·5; N, 20·9%). Since this compound did not correspond with any of the dinitro-4-acetamidodimethylanilines isolated by Hodgson and Crook, it was considered to be 2 : 3-*dinitro-4-acetamidodimethylaniline*. Treatment with hot mineral acid resulted only in the formation of tarry products. (*b*) 3-Nitro-4-acetamidodimethylaniline (0·5 g.) dissolved in hydrochloric acid (3 c.c., *d* 1·2) was treated with nitric acid (1·5 c.c., *d* 1·42) at room temperature. After 30 seconds the solution was made alkaline. The crude product (0·44 g.) contained some unchanged 3-nitro-compound (at least 0·13 g.) which was recovered in the later stages of crystallisation. By a separation similar to that described above there were obtained 2 : 5-dinitro-4-acetamidodimethylaniline (0·14 g., approx. 31%), 2 : 3-dinitro-4-acetamidodimethylaniline (0·04 g., 9%), and a mixture of the two (0·08 g., 18%). (*c*) 2 : 3-Dinitro-4-acetamidodimethylaniline was similarly obtained from the product of nitration of 3-nitro-4-acetamidodimethylaniline with nitrous acid according to the method of Hodgson and Crook (*loc. cit.*).

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UNIVERSITY COLLEGE, SWANSEA. [*Received, December 22nd*, 1945.]

107. *The Further Nitration of* 1 : 3-, 1 : 6-, 2 : 6-, *and* 2 : 7-*Dinitronaphthalenes, and the Preparation of* 1 : 3 : 6-*Trinitronaphthalene.*

By Herbert H. Hodgson and Edward R. Ward.

1 : 3- and 1 : 6-Dinitronaphthalenes both afford 1 : 3 : 8-trinitro- and 1 : 3 : 6 : 8-tetranitro-naphthalenes when further nitrated under the conditions employed by Hodgson, Ward, and Whitehurst (*J.*, 1945, 450) for 1 : 8-dinitronaphthalene. The 1-nitro-group appears to direct nitration to the 8-position exclusively. 2 : 6- and 2 : 7-Dinitronaphthalenes dinitrate readily to give mainly 1 : 3 : 5 : 7- and 1 : 3 : 6 : 8-tetranitronaphthalenes respectively. Mononitration of 2 : 7-dinitronaphthalene to 1 : 3 : 6-*trinitronaphthalene* requires special conditions. The 2-nitro-group appears to direct nitration mainly to the 4-position, and when two β-nitro-groups are present there is simultaneous dinitration to the corresponding *meta* α-positions. The preparation of 2 : 6-dinitronaphthalene from 6-nitro-2-naphthylamine is readily effected by Hodgson and Marsden's method (*J.*, 1944, 22).

When nitrated under conditions identical with those employed for the mono- and di-nitration of 1 : 8-dinitronaphthalene (Hodgson, Ward, and Whitehurst, *J.*, 1945, 450), 1 : 3- and 1 : 6-dinitronaphthalenes both afford 1 : 3 : 8-trinitro- and 1 : 3 : 6 : 8-tetranitro-naphthalenes (cf. Chatt and Wynne, *J.*, 1943, 33, who mononitrated 1 : 3-dinitronaphthalene to 1 : 3 : 8-trinitronaphthalene under different conditions). It is noteworthy that the mono-nitration of both 1 : 3- and 1 : 6-dinitronaphthalenes takes place in the 8-position and not at all in 5- and 3-positions which are *meta* to the existing nitro-groups. This nitration in the *peri* position recalls the predominant nitration of 1-nitronaphthalene in the 8-position, and it would appear that the directing influence in all cases of further nitration of a dinitronaphthalene which contains a 1-nitro-group is exerted by this particular nitro-group (cf. Chatt and Wynne, *loc. cit.*).

In contrast with the above directed mono-nitrations, 2 : 6- and 2 : 7-dinitronaphthalenes both dinitrate very readily to give mainly 1 : 3 : 5 : 7-tetranitronaphthalene and wholly 1 : 3 : 6 : 8-tetranitronaphthalene respectively, thereby indicating the powerful and independent influence of each 2-nitro-group in directing the entering nitro-groups simultaneously into the relevant *meta* positions to them. Owing to the great ease of dinitration, special conditions are necessary for the mononitration of 2 : 7-dinitronaphthalene to 1 : 3 : 6-*trinitronaphthalene*, and we have been unable to isolate a mono-nitrated derivative of 2 : 6-dinitronaphthalene at all, since, even with a deficiency of nitrating acid under varied temperature control, dinitration always occurred. The constitution of 1 : 3 : 6-trinitronaphthalene follows from its conversion by further nitration to 1 : 3 : 6 : 8-tetranitronaphthalene.

A consideration of the possible resonance forms of 2 : 6- and 2 : 7-dinitronaphthalenes indicates that the 4 : 8- and 4 : 5-positions respectively are those which will be the least deactivated by the resonance of the two initial nitro-groups into the various quinonoid positions available (cf. Veselý and Jakes, *Bull. Soc. chim.*, 1923, **33**, 955; Hodgson and Hathway, *J. Soc. Dyers and Col.*, 1945, **61**, 283), and it is in these positions that further nitration occurs.

The preparation of 2 : 6-dinitronaphthalene in *ca.* 50% yield from 6-nitro-2-naphthylamine by Hodgson and Marsden's cobaltinitrite procedure (*J.*, 1944, 22) provides a facile method for obtaining this compound.

Experimental.

Nitration of 1 : 3- *and* 1 : 6-*Dinitronaphthalenes.*—The procedure for the corresponding nitrations of 1 : 8-dinitronaphthalene was followed (Hodgson, Ward, and Whitehurst, *loc. cit.*). In the mononitrations only small amounts of 1 : 3 : 8-trinitronaphthalene separated from the nitration mixture on cooling, and this product, in over 70% yield, was precipitated by pouring on to ice; crystallisation from glacial acetic acid afforded pure 1 : 3 : 8-trinitronaphthalene as established by mixed m. ps. with an authentic specimen. In the dinitrations *ca.* 50% yields of 1 : 3 : 6 : 8-tetranitronaphthalene were obtained, which, in successive crystallisations from glacial acetic acid and acetone, had m. p. 208° (cf. Hodgson, Ward, and Whitehurst, *loc. cit.*, who reported m. p. 207°) (Found : N, 18·4. Calc. for $C_{10}H_4O_8N_4$: N, 18·2%). There remained a small amount of a substance insoluble in acetone, which had m. p. >300°, and appeared to be highly nitrated but not sulphonated since, while it reacted with cold sodium sulphite after the manner of polynitronaphthalenes, it was soluble in hot sodium carbonate but contained no sulphur; it is probably a polynitrohydroxy-compound.

Attempted Mononitration of 2 : 6-*Dinitronaphthalene.*—The 2 : 6-dinitronaphthalene (3 g., m. p. 275°) was suspended in sulphuric acid (8 c.c., *d* 1·84), cooled to 0°, and then treated dropwise below 10°, using vigorous agitation, with a solution of nitric acid (0·85 c.c., *d* 1·42) in sulphuric acid (4 c.c., *d* 1·84), after which the temperature was raised to 30° when nitration commenced and eventually to 75° where it was kept for 5 minutes and then allowed to fall to room temperature. No frothing or oxidation occurred even at 75°. 1 : 3 : 5 : 7-Tetranitronaphthalene (see below) separated during cooling and was the only isolable product.

Dinitration of 2 : 6-*Dinitronaphthalene.*—The dinitro-compound (2 g., m. p. 275°) suspended in sulphuric acid (12 c.c., *d* 1·84) was treated gradually with nitric acid (1·5 c.c., *d* 1·42) in sulphuric acid (1·5 c.c., *d* 1·84) when it passed into solution to reappear after nitration as 1 : 3 : 5 : 7-tetranitronaphthalene. The temperature was allowed to attain 80°, after which the mixture was cooled, and the 1 : 3 : 5 : 7-tetranitronaphthalene filtered off, washed successfully with small amounts of 98% and 50% sulphuric acid, then with water, dried at 100°, and crystallised twice from glacial acetic acid (charcoal), when it melted at 260° (Chatt and Wynne, *loc. cit.*, give m. p. 260°) (Found : N, 18·4. Calc. for $C_{10}H_4O_8N_4$: N, 18·2%). It gave a red-violet solution in hot but not in cold aqueous sodium sulphite (cf. the similar behaviour of 1 : 3 : 8- and 1 : 3 : 6 : 8-tetranitronaphthalenes, Hodgson, Ward, and Whitehurst, *loc. cit.*); the filtrate was rejected.

Mononitration of 2 : 7-*Dinitronaphthalene.*—The dinitro-compound (3 g., m. p. 234°) was suspended in sulphuric acid (14 c.c., *d* 1·84) at 5°, vigorously stirred, and treated dropwise with nitric acid (0·9 c.c., *d* 1·42) in sulphuric acid (3·6 c.c., *d* 1·84) below 10°. The temperature was allowed to rise to 25° when nitration commenced with further rise to 45°, after which the mixture was heated to 80° without any signs of frothing or oxidation. At 70° crystals of 1 : 3 : 6-*trinitronaphthalene* appeared; after the mixture had been cooled to room temperature, these were filtered off, washed, and dried as

above; the compound, recrystallised successively from toluene and 80% aqueous acetone, was obtained in rectangular prisms with facets, m. p. 186° depressed to 158—170° by 1 : 3 : 6 : 8-tetranitronaphthalene (Found: N, 16·2. $C_{10}H_5O_8N_3$ requires N, 16·0%). The filtrate was poured on to ice, and the dark yellow precipitate (2 g.) afforded a further quantity of 1 : 3 : 6-trinitronaphthalene when crystallised from 50% aqueous acetone, the later fractions being unchanged 2 : 7-dinitronaphthalene. 1 : 3 : 6-Trinitronaphthalene readily dissolves in hot aqueous sodium sulphite to an intense red solution, and in acetone it gives a red colour with 10% aqueous potassium hydroxide but only a feeble orange-red colour with boiling sodium carbonate; it is readily soluble in cold toluene in which it tends to form supersaturated solutions, in acetone (in which, however, it is less soluble than 1 : 3 : 6 : 8-tetranitronaphthalene thereby resembling 1 : 3 : 8-trinitronaphthalene), and in hot glacial acetic acid; it is only slightly soluble in hot alcohol.

Dinitration of 2 : 7-*Dinitronaphthalene.*—A suspension of 2 : 7-dinitronaphthalene (5 g.) in cold sulphuric acid (30 c.c., *d* 1·84; it is less soluble in sulphuric acid than the 1 : 8-, 1 : 3-, and 1 : 6-isomers) was nitrated by the procedure employed for 1 : 8-dinitronaphthalene (*loc. cit.*). On addition of the nitrating acid, the temperature rose rapidly but was not allowed to exceed 75°. The 2 : 7-dinitronaphthalene passed into solution; separation subsequently occurred of an intermediate nitration product which itself was redissolved as the temperature increased; on cooling, 1 : 3 : 6 : 8-tetranitronaphthalene separated, and was filtered off, a further quantity being obtained in a less pure condition when the filtrate was poured on to ice. Total yield of pure 1 : 3 : 6 : 8-tetranitronaphthalene, *ca.* 60%. When the nitration was repeated with only 30% excess of nitrating acid over that required for dinitration, the resulting product was mainly 1 : 3 : 6-trinitronaphthalene, the nitration being less violent than in the previous experiment.

Preparation of 2 : 6-*Dinitronaphthalene.*—6-Nitro-2-naphthylamine (7·6 g., 0·05 g.-mol.) was boiled with sulphuric acid (3·5 c.c., *d* 1·84) and water (50 c.c.), the mixture chilled to obtain fine crystals, and then stirred vigorously with a solution of sodium nitrite (3·5 g.) in water (15 c.c.) below 0°. When diazotisation was complete, the solution was stirred into a mixture of finely powdered calcium carbonate (4·5 g.) and crushed ice, a little ether added to remove froth, the liquid filtered, and the filtrate of the neutral 6-nitro-2-naphthalenediazonium sulphate stirred with finely powdered sodium cobaltinitrite (6 g.). A yellow cobaltinitrite complex separated slowly during 20 minutes; it was filtered off and washed with water and ether at the pump (being almost insoluble in either; cf. Hodgson and Marsden, *loc. cit.*). The cobaltinitrite complex reddened rapidly in bright sunlight but could be kept in the dark for at least 24 hours; it was, however, immediately stirred into a solution of sodium nitrite (10 g.) and copper sulphate crystals (10 g.) in water (60 c.c.) containing a suspension of finely divided and freshly prepared cuprous oxide (4 g.). Decomposition was slow at room temperature, so the mixture was raised to 60° and maintained there with stirring for 1 hour, after which it was kept overnight. Water (400 c.c.) was then added, and the precipitate filtered off and washed with water until free from soluble copper salts, dried at 100°, and extracted twice with boiling ethylene dichloride (200 c.c.). The extract was concentrated to very small bulk, and the separated 2 : 6-dinitronaphthalene recrystallised from glacial acetic acid or toluene and purified by sublimation at 230°/15 mm.; it had m. p. 278° (Chatt and Wynne, *loc. cit.*, give m. p. 279°; Veselý and Jakes, *loc. cit.*, give m. p. 268°) (Found: N, 13·0. Calc. for $C_{10}H_6O_4N_2$: N, 12·8%). Yield of pure 2 : 6-dinitronaphthalene, *ca* 50%. 1 : 7-Dinitronaphthalene can be similarly prepared from 8-nitro-2-naphthylamine.

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TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, December 11th*, 1945.]

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108. *Absorption Spectra of Acridines. Part IV. Steric Interference with Ionisation.*

By D. P. CRAIG.

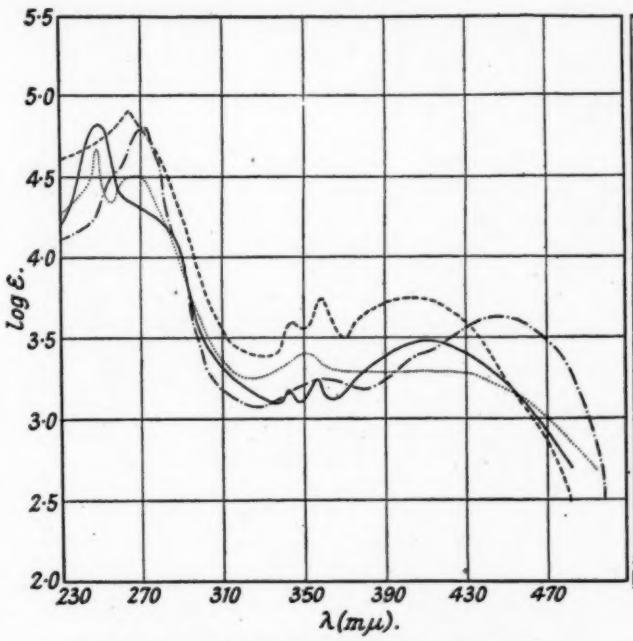
The absorption spectra of 1 : 9-diaminoacridine and 1-amino-9-methylacridine at different pH values are reported. The spectra of the former compound are interpreted to show that it differs from previously investigated mono- and di-aminoacridines in that the ring nitrogen atom is less basic than those of the primary amino groups and is ionised only under very strongly acid conditions. The second compound is shown to form monohydrochlorides involving either the primary amino group or the ring nitrogen, depending on the conditions of ionisation. The case is an unusual one in that a change of solvent causes a reversal in the relative pK values of the two possible ionising processes. The anomalies in ionising behaviour are shown to have their origins in steric hindrance.

ABSORPTION spectra of the mono- and some di-aminoacridines previously reported in Parts I and II (Craig and Short, *J.*, 1945, 419; Turnbull, *J.*, 1945, 441) have established that in all the monoaminoacridines the ring nitrogen is more basic than the nitrogens of the primary amino groups and that it accepts the first proton on ionisation. The evidence provided by the absorption spectra of these compounds is that in the conversion from base to univalent ion the long wave band undergoes a shift towards the red as seen in the ionisation of acridine. On conversion to the bivalent ion, the monoaminoacridines (except the 5-isomeride which does not form a bivalent ion) show a shift to shorter wavelengths giving spectra almost identical with that of the ion of unsubstituted acridine. The inference is that only at the second ionisation is the amino group converted to $-NH_3^{\oplus}$ and thus prevented from participating in the resonance pattern of the structure.

The results for 1 : 9-diaminoacridine and for 1-amino-9-methylacridine are shown in Figs. 1—4 and in the Table.

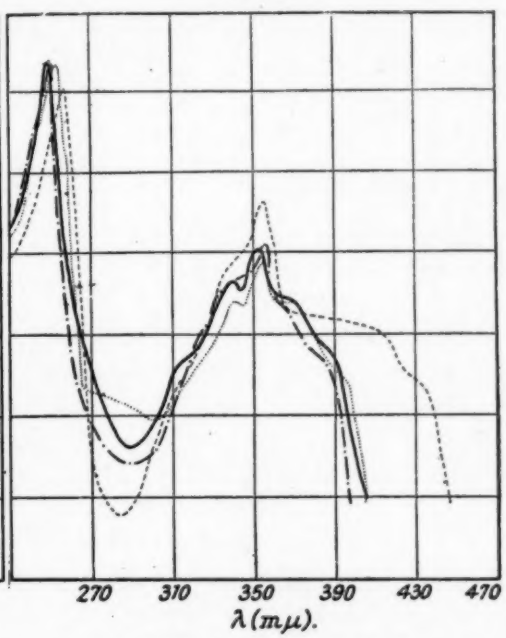
Dealing first with 1 : 9-diaminoacridine, the absorption in 5N-hydrochloric acid reverts almost exactly to that of acridine itself (not, like other aminoacridines, to that of the acridine *ion*) as shown in Fig. 2. The indication is that the two amino groups are not able to participate in the resonance (*i.e.*, are ionised to $-NH_3^{\oplus}$) and that the ring nitrogen is behaving as it does in acridine; the ring nitrogen, then, is not ionised in 5N-hydrochloric acid. The conclusion that in 1 : 9-diaminoacridine the ring nitrogen is the *least* basic is confirmed by the observation (Fig. 3) that in 18N-sulphuric acid the absorption is almost identical with that of the acridine

FIG. 1.



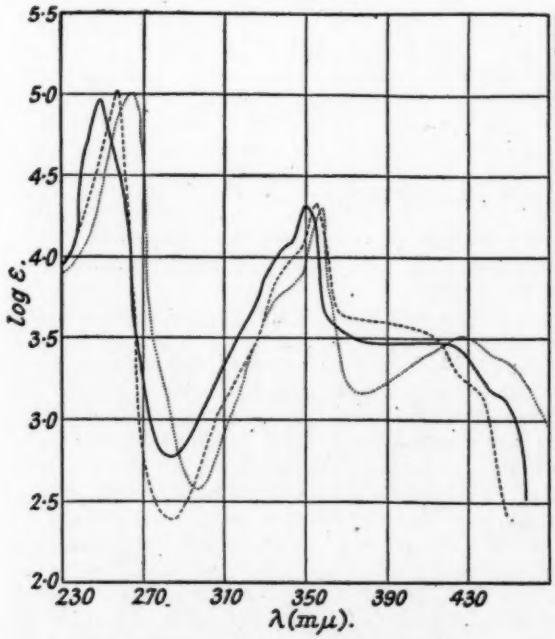
——— 1-*Amino*-9-*methylacridine in abs. alcohol.*
—·—·— 1 : 9-*Diaminoacridine in abs. alcohol.*
– – – – – – 1-*Aminoacridine at* pH 11 *in* 33% *methanol–water.*
····· 1 : 9-*Diaminoacridine at* pH 3·0.

FIG. 2.



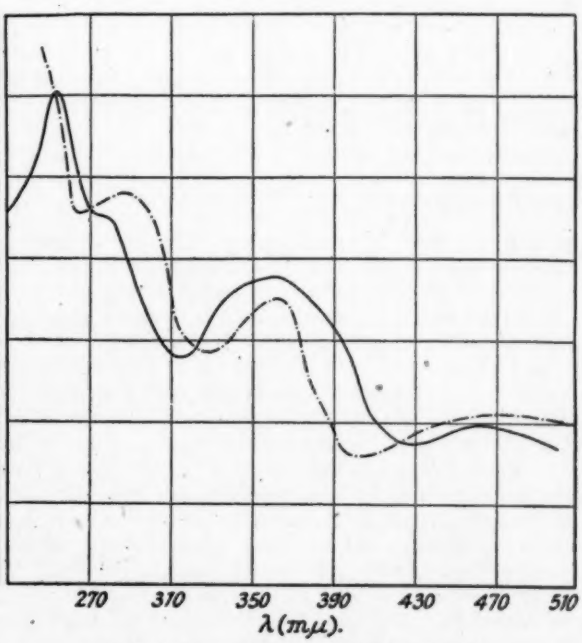
——— 1 : 9-*Diaminoacridine in* 5N-HCl.
—·—·— *Acridine at* pH 11.
····· 1-*Amino*-9-*methylacridine in alcoholic* N/15-HCl.
– – – – – – *Acridine ion in* 5N-HCl.

FIG. 3.



——— 1 : 9-*Diaminoacridine in* 18N-H_2SO_4.
····· 1-*Amino*-9-*methylacridine in* 5N-HCl.
– – – – – – *Acridine in* 5N-HCl.

FIG. 4.

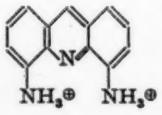


——— 1-*Amino*-9-*methylacridine in* 0·25N-HCl.
—·—·— 1-*Aminoacridine at* pH 2·5 (33% *methanol–water*).

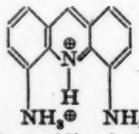
Absorption maxima and significant inflexions.

	$\lambda_{max.}$, mμ.	log ε.	$\lambda_{max.}$, mμ.	log ε.	$\lambda_{max.}$, mμ.	log ε.
			1 : 9-*Diaminoacridine.*			
In abs. alcohol	272	4·80	362	3·22	448	3·63
At pH 3 (33% methanol)	250	4·62	352	3·42	420	(Inflexion)
	268	4·51				
At pH 2·5 (33% methanol)	248	4·9	354	3·75	420	(Inflexion)
	268	4·28				
In 5N-HCl	249	5·17	353	4·03	(No band)	
In 18N-H_2SO_4	250	4·98	352	4·31	410	(Inflexion)
			1-*Amino-9-methylacridine.*			
In abs. alcohol	252	4·82	358	3·25	413	3·50
N/15-HCl in abs. alcohol	254	5·17	354	3·95	(No band)	
N/4-aqueous HCl	255	5·02	360	3·88	460	2·97
	278	(Inflexion)				
5N-HCl	264	5·01	358	4·31	426	3·50

ion. It is only under these extreme conditions of hydrogen-ion activity that the ring nitrogen accepts a proton.

(I.) 

1 : 9-Diaminoacridine in 5N-HCl.

 (II.)

1 : 9-Diaminoacridine in 18N-H_2SO_4.

The addition of half an equivalent of hydrochloric acid to 1 : 9-diaminoacridine (M/300) gives a pH of 3·65 (in 50% alcohol, Albert and Goldacre, unpublished); if this result, suitably corrected for hydrolysis, were taken to be the pK_a of the ionisation it would correspond with the ionisation of a primary amino group: the remaining resonating system should then be the same as that of 1-aminoacridine. When the spectrum of 1-aminoacridine is compared with that of 1 : 9-diaminoacridine at pH 3·0 in Fig. 1, the agreement is poor, and the curves suggest strongly the existence of a mixture of base, univalent ion, and bivalent ion. It is in any case likely that the first and second basic constants would lie rather close together since the ionisation of one of the amino groups should not greatly affect the free energy change involved in the ionisation of the second amino group. The pH 3 absorption, then, is due to a mixture of base, bivalent ion, and a little univalent ion. That there is some of the latter present is shown by the fact that the pH 3 curve cannot be obtained exactly by linear combination (from a linear plot in ϵ) only of the base and bivalent ion curves, but requires the addition of a small percentage of the 1-aminoacridine curve.

1-Amino-9-methylacridine shows no special features in absolute alcohol solution (free base, Fig. 1) or in 5N-hydrochloric acid (bivalent ion, Fig. 3). However, two different univalent ions exist. In alcoholic N/15-hydrochloric acid the spectrum corresponds with that of acridine, indicating that the primary amino group is ionised and the ring nitrogen not ionised (Fig. 2). In aqueous N/4-hydrochloric acid, the spectrum is close to that of the univalent ion of 1-aminoacridine in which it is the ring nitrogen which is ionised (Fig. 4) and the primary amino group free. The $-NH_3^{\oplus}$ univalent ion is also obtainable to a small extent in very dilute aqueous hydrochloric acid, and there is a small concentration range within which the $-NH_3^{\oplus}$ form is stable in the cold and the $-\overset{\oplus}{N}=$ form in the hot solution. A striking feature of the present case is the fact that a proton shift of at most 2A., involving a very small overall energy change, causes so sweeping a change in the energy levels of excited states as reflected in the absorption spectrum.

Methyl-substituted aminoacridines having either the 1- or 9-position free differ to a negligible extent from the unsubstituted aminoacridine in their ionisation behaviour (Albert and Goldacre, unpublished). The anomalous ionisation of 1-amino-9-methylacridine in very dilute alcoholic acid is almost certainly due to steric hindrance to the close approach of an oxonium (or ethyloxonium) ion to the ring nitrogen atom. The primary amino group is accordingly ionised first. The case is an unusual one in that a change of solvent causes a reversal of the relative pK values of the two possible ionising processes.

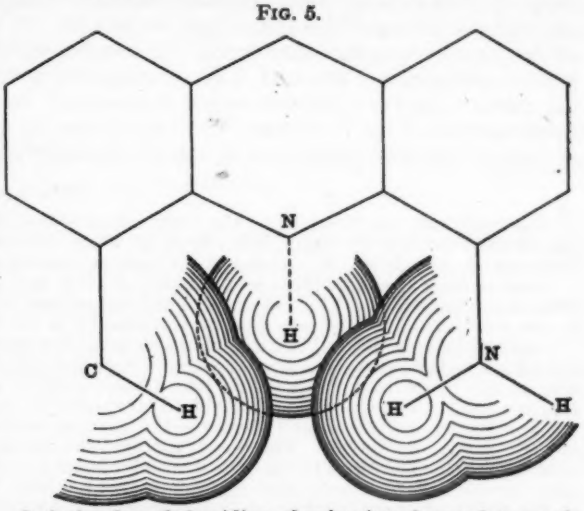
In 1 : 9-diaminoacridine the steric consideration is still more serious, even though the path of access to the ring nitrogen is faintly wider (see Fig. 5). Here the two amino groups are ionised at about the same pH value, and the approach of oxonium ions to the ring nitrogen is then hindered both by a steric effect and by the electrostatic repulsion of the two $-NH_3^{\oplus}$ groups to the approaching oxonium ion. The ring nitrogen atom is not ionised in 5N-hydrochloric acid but accepts a proton in 18N-sulphuric acid.

The steric implications in the case of 1-amino-9-methylacridine are illustrated in Fig. 5. The diagram has been drawn using the bond lengths of Pauling and Huggins (*Z. Krist.*, 1934, **87**, 205) as modified by Schomaker and Stevenson (*J. Amer. Chem. Soc.*, 1941, **63**, 37). The situation can also easily be visualised for 1 : 9-diaminoacridine. The effect of the ionisation of one primary amino group on the ionisation of the other in this substance is expected to be similar to that studied in some dicarboxylic acids (Gane and Ingold, *J.*, 1928, 1594). Since the resonance interaction between the 1- and 9-positions is small, the ruling effect should be the decrease in

active mass of oxonium ions in the vicinity of the second amino group due to electrostatic repulsion by the $-NH_3^{\oplus}$ group. The centres of the amino groups are about 5 A. apart, and the second amino group should differ in pK_a value by about one unit from the first on this count (Bjerrum, *Z. physikal. Chem.*, 1923, **106**, 219).

As far as the ring nitrogen is concerned, the process of ionisation involves the approach of an oxonium ion sufficiently close to the basic centre to enable the exchange of a proton to take place between the two. For this to be possible the proton must, in general, be transported up to about 1·5 A. from the nitrogen atom, *i.e.*, to about the hydrogen bond distance. Fig. 5, however, shows that the undistorted configuration would allow an approach no nearer than 3·5 A. in the plane of the molecule, and the required proximity will be attained only by energetic oxonium ions or at instants when the configuration is distorted by favourable vibrations. Approach to the nitrogen atom from directions out of the plane is not so difficult sterically, but is less likely to result in the formation of an N–H bond since the available *n* orbital is directed mainly in the plane of the rings. It seems reasonable to postulate that the low basicity of the ring nitrogen in 1 : 9-diaminoacridine and 1-amino-9-methylacridine is a steric effect and results from the blocking of approaching oxonium ions by the 1- and 9-groups.

FIG. 5.



1-Amino-9-methylacridine, showing interference between the Van der Waals spheres of the 1- and 9-subsituents and the hydrogen attached to the nuclear nitrogen.

EXPERIMENTAL.

The spectra were observed using a Hilger medium quartz spectrograph with a tungsten spark as light source. The pH 3·0 buffer solution used was a sodium citrate–HCl mixture made up in 33% methanol (International Critical Tables, Vol. 1) and the pH value measured with a glass electrode. The stated value is uncorrected for the effect of alcohol on the electrode.

Grateful acknowledgment is made to Dr. Adrien Albert for the 1-amino-9-methylacridine and for much helpful discussion; also to Dr. F. Lahey for the 1 : 9-diaminoacridine.

CHEMISTRY DEPARTMENT, UNIVERSITY OF SYDNEY. [*Received, November 26th*, 1945.]

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109. *The Self-diffusion of Lead in Lead Sulphide.*

By J. S. ANDERSON and J. R. RICHARDS.

Some preliminary measurements of the self-diffusion of the lead ion in lead sulphide have been made between 733° K. and 1043° K., the radioactive isotope Ra-*D* being used as tracer. A modified technique, particularly suited for the measurement of diffusion coefficients not less than *ca.* 10^{-13} cm.^{2} sec.$^{-1}$ in compressed powder specimens, is described. Under standardised conditions, the diffusion is represented by $D = 1{\cdot}4\ e^{-42{,}000/RT}$, but evidence is presented that *D* depends upon small variations in the stoicheiometric Pb : S ratio. The relation between self-diffusion coefficient and the nature and concentration of lattice defects is discussed, and from the relationship between *D* and the Pb : S ratio, the presence of Schottky defects is inferred.

MEASUREMENTS of the rate of self-diffusion of lead in lead sulphide were undertaken originally in order to obtain data concerning the diffusion process in a typical polar solid built up from bivalent ions. Many experimental studies on reactions in oxide and sulphide systems have been made in recent years, but knowledge of the fundamental processes underlying reaction is still very scanty. One aspect of this problem, to which our attention had been drawn in the course of measurements on the relation between stoicheiometric deficiency and semi-conducting properties of stannous and lead sulphides (Anderson and Morton, *Proc. Roy. Soc.*, 1945, *A*, **184**, 83; Morton, unpublished), is the readiness with which a crystal lattice can attain thermodynamic equilibrium with respect to lattice defects. Lattice " holes " are necessarily created at the surface, but should ultimately be distributed at random throughout the lattice through the occurrence of self-diffusion.

Lead sulphide appeared to be a very suitable compound for study, since diffusion measurements could be made by the radioactive indicator method. For reasons set out below, however, our measured diffusion coefficients cannot be regarded as true material constants. Nevertheless, the results seem worth setting on record, since they reveal an effect which is not only of interest for the statistical mechanical model of the solid state, but is undoubtedly important in reaction processes between solids at elevated temperatures. This effect arises from that variability in stoicheiometric composition which, in principle, is common to all solids of atomic lattice type (cf. Schottky and Wagner, *Z. physikal. Chem.*, 1930, *B*, **11**, 163; Fowler and Guggenheim, " Statistical Thermodynamics," Cambridge, 1940, pp. 549—554), and is particularly marked in the case of the heavy-metal sulphides.

Whereas most previous workers on self-diffusion have measured only the decrease in radioactivity at the surface of the specimen, due to the occurrence of diffusion (cf. Hevesy and Seith, *Z. Physik*, 1929, **56**, 790; Seith, *Z. Elektrochem.*, 1933, **39**, 538; Mackay, *Trans. Faraday Soc.*, 1938, **34**, 845), we measured the concentration gradient of the radioactive isotope (Ra-*D*) directly. We found thereby that the self-diffusion coefficient was not constant with depth. This effect, which can be correlated with minute changes in the stoicheiometric composition of the solid, was not recognised until most of the experimental work was complete, although the relation between stoicheiometric composition and self-diffusion coefficient should have been foreseen. Previous workers have—permissibly in most cases, no doubt—ignored it. It is evident that the determination of true self-diffusion coefficients in non-stoicheiometric solids entails very considerable difficulties.

Experimental.

Lead sulphide was prepared by the direct union of lead (B.D.H. assay quality) with sulphur, purified as described by Bacon and Fanelli (*Ind. Eng. Chem.*, 1942, **34**, 1043). Details of the method are given by Ridge and Anderson (*Trans. Faraday Soc.*, 1943, **39**, 93). Some of the later measurements were made on resublimed lead sulphide.

Radioactive Lead Sulphide.—As no source of Th-*B* was available, we extracted Ra-*D* from the active deposit in old glass radon capillaries. The crushed capillaries were leached with 5N-nitric acid, and 0·1 g. of pure lead nitrate was added to the solution. The lead was deposited anodically as peroxide and subsequently precipitated as sulphide.

Lead Sulphide Pellets.—For the measurements, the finely powdered (inactive) lead sulphide was compressed into cylindrical pellets, 8 mm. in diam. and 4—7 mm. thick, in a hardened steel die, between plungers ground truly plane and square to the axis. The pellets had a black metallic lustre, and were strong enough to be handled without any loss in weight. The space-filling amounted to 90—95%.

Application of Radioactive Indicator.—For each measurement, one pellet was coated on one end face with a deposit of the radioactive sulphide. This was evaporated in a vacuum (10^{-4} mm.) from a small electrically heated oven, provided with collimating apertures to limit the molecular beam to a small solid angle. The pellet was held in place behind a mica disc, provided with a central hole of diameter just less than that of the pellet. By this means, contamination of the side of the pellet with radioactive sulphide vapour was avoided. Conditions yielding deposits with the optimum initial activity (deposits about 0·4—0·9μ thick) were found by trial and error. Ra-*E* sulphide sublimed more readily than Ra-*D* sulphide, but owing to the short half-life of Ra-*E*, the initial count of fairly thick deposits soon settled down to a steady value.

Diffusion Measurements.—Two pellets, one of them bearing the radioactive deposit, were clamped tightly, end to end, between graphite discs, in a small steel press. The graphite prevented direct contact between the sulphide and the metal, with consequent reduction at high temperatures. The press was heated in an evacuated silica tube, in an electric furnace fitted with a rough thermostatting device.

Even at the lowest temperature employed, some volatilisation of lead sulphide occurred, and there was some loss of radioactive sulphide from this cause. Photographic investigation of a pellet, sectioned lengthways, showed that a very low concentration of active material had covered the entire outer surface, although in amount too small to affect the counter measurements. Superficial sulphiding of the press was observed, due (as discussed below) to evaporation of sulphur out of the sulphide.

After being heated, the two pellets were separated and embedded in " Perspex " resin, according to the procedure employed for setting metallographic specimens. The end face of the pellet, from which diffusion had occurred, was placed flat upon the base of the mould, so that it was ultimately flush with and parallel to one surface of the " Perspex " disc. The purpose of embedding the pellet was to enable thin parallel cuts to be made from the pellet with ease and precision. It is hardly possible to grind down the face of a pellet (8 mm. diam.) without producing curvature of the surface and obliquity to the axis, but the " Perspex " disc (21 mm. diam.) provides a bearing surface of sufficient size to ensure that the central region remains truly flat. The rear surface was first lapped on coarse carborundum paper until the thickness was uniform to within 0·01 mm. all over, as measured with a micrometer at four marked positions round the cylinder. Between successive radioactive counts, the front surface was lapped down on wet 360-mesh carborundum paper. At each step, two sets of four micrometer readings were made; the average of each set never varied by more than 0·002 mm., and in any one step the deviation from parallelism with the original surface did not exceed 0·005 mm. Any such deviation was corrected at the next step. This procedure enabled the concentration gradient to be measured at several different levels below the original surface, even though the depth of penetration was very small; *e.g.*, in one pellet (No. 14) six steps were measured within 0·064 mm. of the original surface, and the steep fall within the first 0·02 mm. was clearly shown.

Counting Technique.—An argon–alcohol filled Geiger–Müller counter was used, without a scaling circuit; this limited adversely the maximum activity that could be recorded. The thin window of the counter actually admitted only the β-rays from Ra-*E*, not those of Ra-*D*; due time was therefore given before measurement, to establish radioactive equilibrium between Ra-*D* and Ra-*E*. Counter and pellet were brought always into the same relative positions.

Evaluation of Results.—The arrangement used, in which Ra-*D* diffused roughly symmetrically from a thin layer into the underlying and superimposed pellets, corresponds to the case of diffusion from a finite source along an infinite cylinder (cf. Barrer, " Diffusion in and through Solids," Cambridge, 1942, p. 45). The particular solution of the Fick equation for this case is

$$c_x = \frac{Q}{\sqrt{\pi Dt}} e^{-x^2/4Dt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where Q = amount of diffusion material originally deposited, c_x = concentration at the distance x from the original surface after the time t, and D = diffusion coefficient.

The measured radioactivity corresponds, not to that of the radioactive material on the exposed surface, but to the integrated effect of β-radiation issuing, subject to the exponential absorption law (coefficient = k), from all depths. If, in a column of unit area, the concentration of radioactive material between x and $(x + dx)$ from the surface be c_x, it contributes an amount proportional to $c_x \cdot e^{-kx} \cdot dx$ to the radioactive count at the surface. Then the total activity A_0 measured at the surface is given by

$$A_0 = \frac{Q}{\sqrt{\pi Dt}} \int_0^\infty e^{-(x^2/4Dt + kx)} dx \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Similarly, if the surface has been lapped down to a depth x_1 below the original level, the new activity is

$$A_{x_1} = \frac{Q}{\sqrt{\pi Dt}} \int_x^\infty e^{-(x^2/4Dt + kx)} dx \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Changing the variable, writing

$$y = x/\sqrt{4Dt} + h\sqrt{Dt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and integrating between the limits $y = y_0 = h\sqrt{Dt}$ and $y = \infty$, we transform (2) into

$$A_0 = \frac{2Q}{\sqrt{\pi}} e^{h^2Dt} \int_{y_0}^{\infty} e^{-y^2} dy = Q \cdot e^{h^2Dt}(1 - \text{erf } y_0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Similarly for (3),

$$A_{x_1} = Q \cdot e^{h^2Dt}(1 - \text{erf } y_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Hence

$$A_{x_1}/A_0 = (1 - \text{erf } y_1)/(1 - \text{erf } y_0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

As a means of combining measurements, we may notice that erf $y_0 < 1$, so that if $A_x/A_0 \ll 1$ (as it is for measurements made at any appreciable depth below the original surface), (7) reduces approximately to

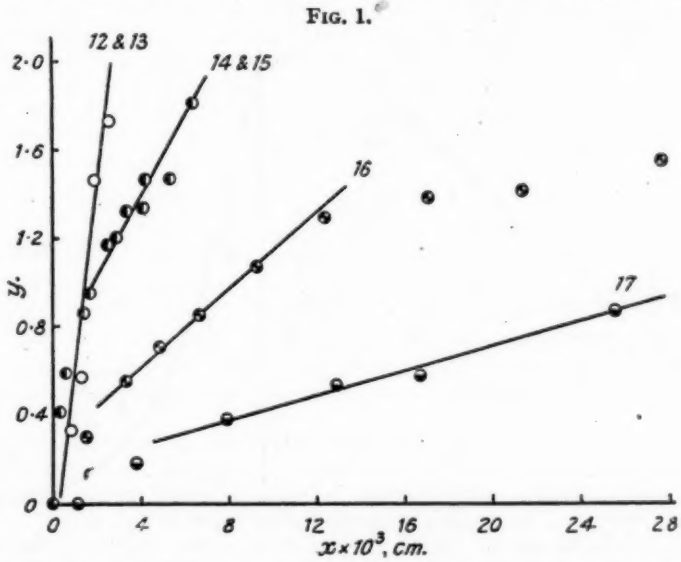
$$\text{erf } y = 1 - A_x/A_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Values of y obtained from probability tables may be plotted against x; the resulting graph should be asymptotic to a straight line of slope $1/\sqrt{4Dt}$. Alternatively, for each depth x, the appropriate value of A_x/A_0 may be used to solve (7) by successive approximation.

Results and Discussion.

The experimental measurements were first treated by the approximate graphical method outlined above, thereby obtaining smoothed values for the diffusion coefficient on the assumption that the error-function

Fig. 1.



distribution of radioactive isotope was valid. Plots of y against x [equation (8)] are given, for the main series of experiments only, in Fig. 1. The following table gives the corresponding values of D.

$T°$ K.	733°	833°	938°	1043°
D, cm.² sec.⁻¹	$4{\cdot}3 \times 10^{-13}$	$2{\cdot}2 \times 10^{-11}$	$1{\cdot}3_8 \times 10^{-10}$	$1{\cdot}4 \times 10^{-9}$
Time of diffusion expt., hours	265	97·5	71	67

In Fig. 2, log D is plotted against the reciprocal of the temperature; the results fall fairly well on the line $D = 1{\cdot}3_8\, e^{-42{,}000/RT}$.* The activation energy of diffusion, 42,000 cals., is comparable with that found for lead in lead chloride and iodide.

These values for the diffusion coefficient prove to be self-consistent chiefly because they were obtained under standardised experimental conditions. Further analysis shows that they are not true constants of the material.

If the apparent diffusion coefficient corresponding to the radioactive count at each depth be calculated from (7) by successive approximation, the result is less satisfactory: D varies continuously with depth; the radioactive isotope is not distributed according to the error-function law. Using the values of D from the above table, calculation of the ratio A_x/A_0 for various values of x shows how the radioactive count would vary with depth x if the error-function distribution were obeyed. In Fig. 3 such a curve is compared with the experimental data for the 833° K. pellet, the co-ordinate scales being adjusted so that the curves coincide at the two points for which $A_x/A_0 = 1$ and $\frac{1}{2}$ respectively. It may be seen that the apparent diffusion constant must be relatively *too small* close to the original surface, and *too large* at greater depths. The same is true for all the diffusion experiments carried out as described above. For the pellet A, in which diffusion occurred under different conditions (see below), agreement with the error-function curve is better, but deviation occurs in the opposite sense.

These results can be correlated with the possibility of departure from the ideal Pb : S ratio. Lead sulphide, like many of the chalcogenides of the heavy metals, is a " non-stoicheiometric " compound; *i.e.*, the PbS

crystalline phase is stable over a limited range of composition on either side of the ideal Pb : S ratio. There is apparently no recorded evidence that variability of composition has been detected analytically (it is, in any case, unlikely that so familiar a compound has been subjected to critical analysis since analytical technique was adequate to reveal small variations); nevertheless, it is clearly indicated by the semiconducting properties of the compound (cf. Hintenberger, *Z. Physik*, 1942, **119**, 1, whose results have been confirmed by one of our colleagues). Prepared by our method, lead sulphide contains a small stoicheiometric excess of sulphur. If the partial pressure of sulphur vapour be kept low (*e.g.*, absorption of sulphur by another metal in the gas space), the excess of sulphur would be progressively lost during heating, and lead sulphide with a stoicheiometric excess of lead would ultimately result. This could and did occur under the conditions of our main series of experiments. At the temperatures of the experiments, diffusion was slow, so that a composition gradient, changing with time, must have been set up in the outer portion of each pellet. If the self-diffusion coefficient is dependent on the stoicheiometric composition, no true solution of the Fick equation can be found for such ill-defined conditions.

Variation in Self-diffusion Rate with Changes in Stoicheiometric Composition.—The general model for diffusion and allied processes in crystals is based on Schottky and Wagner's theory (*loc. cit.*) of " ordered mixed phases." In developing the theory of diffusion, Wagner (*Z. physikal. Chem.*, 1931, Bodenstein Festb., p. 186) stated that the self-diffusion constant must be a function of the composition, but did not elaborate the problem. Our measurements provide the first opportunity to put the matter to a qualitative test.

FIG. 2.

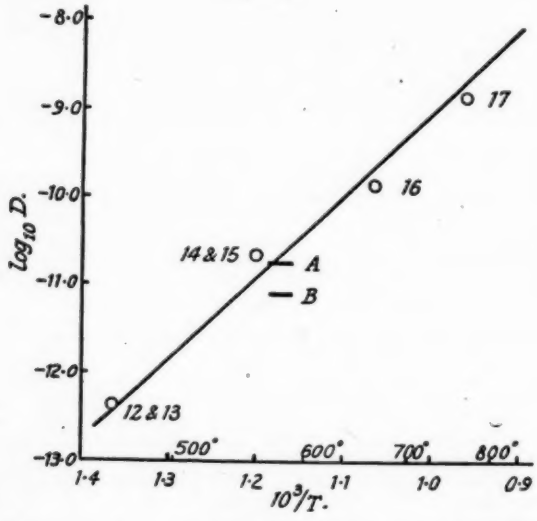
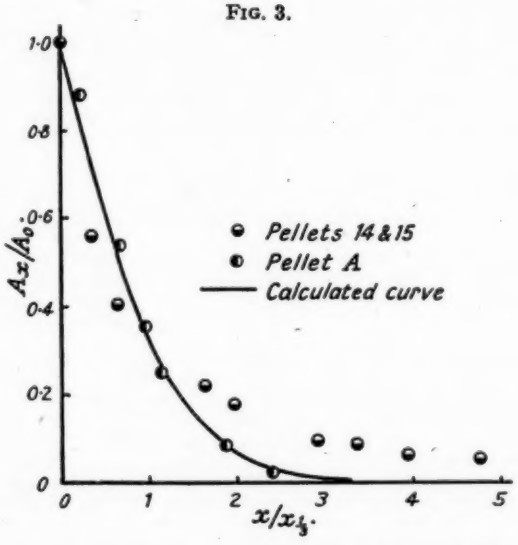


FIG. 3.



In thermodynamic equilibrium at temperatures above the absolute zero, a crystal lattice must contain a certain concentration of lattice defects—atoms in interstitial positions, or vacant lattice sites. The process of self-diffusion represents the random migration of these defects through the crystal lattice. The effect of changes in stoicheiometric composition may be foreseen by considering the alternative mechanisms discussed by Wagner. We may recognise two cases that can arise.

Case A. The stoicheiometric compound AX contains predominantly defects of Frenkel type : with one species of ion (most probably the A cations) in interstitial positions, and vacant sites in the corresponding lattice. This model has been shown to be valid for *e.g.*, silver bromide. If we denote by N_A^h, N_A^i the number of vacant cation sites and interstitial cations respectively, we have in the stoicheiometric compound $N_A^{h*} = N_A^{i*}$ (symbols relating to the stoicheiometric phase being marked with an asterisk), and we may recognise two partial processes operative in self diffusion : (i) diffusion of ions between adjacent interstitial positions, with activation energy U^i; (ii) diffusion of cation holes, *i.e.*, the jump of a cation into an adjacent vacant cation site, with activation energy U^h. The corresponding partial self-diffusion coefficients are $D^{i*} = kN_A^{i*}e^{-U^i/kT}$ and $D^{h*} = kN_A^{h*}e^{-U^h/kT}$. The relative importance of these will not be equal, since we may in general expect that $U_A^i \neq U^h$. Departure from stoicheiometric composition occurs when $N_A^h \neq N_A^i$. For a crystal containing an excess of metal, $N_A^i > N_A^{i*}$, $N_A^h < N_A^{h*}$. If the concentration of defects in the lattice of the stoicheiometric compound is small, the number of defects introduced by even a minute change of composition can far outweigh those present in thermal equilibrium; *i.e.*, $N_A^i \gg N_A^{i*}$, $N_A^h \longrightarrow 0$. Conversely, for an appreciable excess of non-metal, $N_A^h \gg N_A^{h*}$, $N_A^i \longrightarrow 0$. Thus, with increasing departure from ideal composition, one or other component of the diffusion process becomes predominant. At the same time, the partial self-diffusion coefficients change; thus, on the metal-rich side, $D^i = (N_A^i/N_A^{i*})D^{i*}$; $D^h \longrightarrow 0$. The resultant effect of any appreciable change in composition is that the increase in one partial diffusion coefficient more than compensates for the decrease in the other; the net self-diffusion rate must therefore increase with rising

departure from stoicheiometry on both sides of the ideal formula, the self-diffusion coefficient being at a minimum at some temperature close to, but not necessarily identical with, the ideal composition. The case is essentially similar to the effect of anomalous solid solution on the ionic conductivity of polar crystals, discussed by Koch and Wagner (*Z. physikal. Chem.*, 1938, *B*, **38**, 295).

Case B. The stoicheiometric compound contains defects of Schottky type—vacant sites in both cation and anion lattices, but no interstitial ions. Then $N_A^{h*} = N_X^{h*}$. For self-diffusion of the cations there is then only the one process—migration of vacant sites, with the self-diffusion coefficient $D^{h*} = k'N_A^{h*}e^{-U^h/kT}$. For this type of crystal phase, deviation from stoicheiometric composition arises if $N_A^h \neq N_X^h$; increase in the partial pressure of, *e.g.*, the non-metal in equilibrium with the crystal results in building additional X atoms on to the lattice, N_A^h increasing and N_X^h decreasing thereby. It follows that changes in composition must be reflected in a monotonic change in the self-diffusion rate for the cation A; D must increase with increasing excess of non-metal, and diminish asymptotically to zero with increasing excess of metal.

It follows, therefore, that the effect of variability of composition upon self-diffusion rate should be detectable. It remains to be shown that it underlies our own experimental observations. To this end, we sealed up a pair of pellets, prepared for diffusion to occur, in each of two Pyrex tubes; no metal was present, the pellets being pressed into contact by glass-enclosed weights, which filled the tubes except for a dead space of about 5—6 c.c. All pellets were made from a sample of resublimed lead sulphide. The tubes were heated for 52½ hours at 853° ± 10° K. Tube A contained 0·5 mg. of pure sulphur, giving about 60—80 mm. pressure of S_2 vapour during the experiment; tube B was evacuated. In B a minimal change of stoicheiometric composition should have occurred during heating, whereas in A the composition gradient should have been the reverse of that set up in the main series, with the sulphur-richest material on the exterior of the pellet. The diffusion constants (D, in cm.² sec.⁻¹) calculated by the graphical method for these two experiments were: Pellet A, $2{\cdot}3 \times 10^{-11}$; Pellet B, $7{\cdot}9 \times 10^{-13}$. That of Pellet A is significantly greater, as predicted.

In the following table, the trend of diffusion coefficients is compared with depth in pellet A and in one of the pellets of the main series respectively.

Pellet A. Excess of sulphur decreasing inwards. 843 ± 10° K.	x, cm. × 10³	0·6	1·9	2·6	3·1	5·2	6·6
	D, cm.² sec.⁻¹ × 10¹¹	33·0	6·1	4·0	3·4	4·0	3·3
Pellet 14. Lead excess decreasing inwards. 833° K.	x, cm. × 10³	0·3	1·7	2·9	4·1	5·3	6·4
	D, cm.² sec.⁻¹ × 10¹¹	0·04	0·3	0·5	0·9	1·3	1·2

Note.—Because of the departure from the true error-function law, diffusion coefficients calculated from individual points are not identical with those derived from the graphical method, though of the same order of magnitude.

The self-diffusion coefficient, from these data, appears to vary monotonically with composition. We conclude that lead sulphide contains lattice defects of predominantly Schottky type. The values of D approach asymptotically to a constant value, which may be taken as characteristic of the particular sample of material composing the pellet.

The compressed powder pellets must, necessarily, have possessed a large internal surface. It is therefore relevant to enquire whether bulk diffusion or surface diffusion was observed in these experiments. The occurrence of both bulk and surface diffusion might, in fact, simulate a rise of D with increasing depth below the original surface, as observed in the main series of experiments; † it could not, however, account for the reversal of this trend under conditions where excess sulphur could be incorporated in the crystal lattice (Pellet A). Moreover, it is significant that diffusion assumes a just conveniently measurable magnitude at 460° C., being 0·53 of the absolute melting point of lead sulphide (T_m = 1112° C.). According to Tammann's rule, "Platzwechsel" processes in solids become detectable at $0{\cdot}52$—$0{\cdot}57T_m$, as indicated by the onset of fritting (Tammann, *Z. anorg. Chem.*, 1926, **157**, 321). For lead sulphide, Tammann and Kordes (*ibid.*, 1925, **149**, 62) give 470° C. as the fritting temperature. Although any criterion of "perceptible diffusion" is arbitrary, the Tammann rule is in substantial agreement with the temperatures of incipient reactivity of solids (cf. the work of Hedvall and of Hüttig, particularly Hüttig, *Z. Elektrochem.*, 1935, **41**, 527; *Angew. Chem.*, 1940, **53**, 35; *Kolloid-Z.*, 1942, **98**, 6, 263). Tammann (*Z. anorg. Chem.*, 1925, **149**, 67) found the reaction temperature of the reaction PbS + CdO ⟶ PbO + CdS to be 440° C. Further, the onset of recrystallisation in solids, as shown by Hahn's emanation method (cf. Hahn and Senftner, *Z. physikal. Chem.*, 1934, **170**, 191; Schröder and Schmäh, *Z. Elektrochem.*, 1942, **48**, 248), is at about the same fraction of the absolute melting point. The physical significance of the Tammann rule is that the mean diffusion path shall be sufficiently large to produce sensible effects within some interval of time determined by the type of criterion employed experimentally. For fritting experiments, such as those of Tammann and Kordes, this requires that D shall be of the order 10^{-13} cm.² sec.⁻¹, *i.e.*, about that found by us at the temperature $0{\cdot}53T_m$. This agreement is evidence that bulk diffusion was actually measured in our experiments.

The authors express their indebtedness to the Director of the Commonwealth Radium Laboratory, Dr. C. E. Eddy, for the provision of radon residues, and to Dr. H. Rathgeber for much advice in connection with the radioactive measurements.

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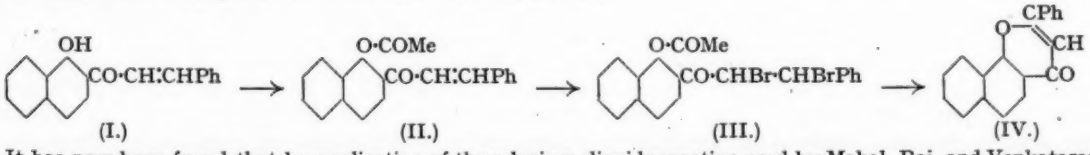
† Three experimental points belonging to Pellet 16, which have been neglected in Fig. 1, fall on a second line, indicative of a higher diffusion coefficient, and may perhaps represent a surface diffusion process.

NOTES.

A New Preparation of 7 : 8-*Benzoflavone* (*α-Naphthaflavone*). By F. E. Smith.

7 : 8-Benzoflavone (IV), which is used as a fluorescent indicator in halogenometry, has hitherto been prepared from 2-cinnamoyl-1-naphthol (I) by acetylation to (II) followed by bromination to the dibromide (III) and subsequent treatment with potassium hydroxide (Kostanecki, *Ber.*, 1898, **31**, 705).



(I.) (II.) (III.) (IV.)

It has now been found that by application of the selenium dioxide reaction used by Mahal, Rai, and Venkataraman (*J.*, 1935, 866) 7 : 8-benzoflavone (IV) can be prepared from 2-cinnamoyl-1-naphthol (I) in one stage, giving a yield of 84·3%. This high yield is surprising in view of the fact that Mahal *et al.* (*loc. cit.*) obtained much lower yields (43·7% of flavone from 2-cinnamoylphenol and 35·2% of 7-benzyloxyflavone from 5-benzyloxy-2-cinnamoylphenol).

2-Cinnamoyl-1-naphthol (m. p. 124°) (8 g.) was mixed with selenium dioxide (8 g.) and placed in a flask fitted with sealed stirrer and reflux condenser. Amyl alcohol (80 ml.) was added and the mixture was gently refluxed while stirring for twelve hours. When the mixture had cooled the selenium was removed by filtration and washed with a little amyl alcohol. The filtrate was subjected to steam distillation, the volume being maintained constant in the flask. When all the amyl alcohol had been removed the flask and contents were cooled with shaking to prevent solidification of the product on the wall of the flask. The crude solid was collected and dried (6·7 g., m. p. 148—150°). It was crystallised from 100 ml. of spirit to give 5 g. of brown-yellow plates, m. p. 155—156°. Concentration of the mother liquor led to the recovery of 1 g., m. p. 148°.

I am indebted to the Directors of Herts Pharmaceuticals, Ltd., in whose laboratories the work was carried out, for permission to publish this note.—71 Ealing Village, London, W.5. [*Received, December 6th*, 1945.]

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4 : 4′-*Dinitrodiphenylsulphone*. By H. Burton and W. A. Davy.

In attempts to determine whether crude 4 : 4′-dinitrodiphenyl disulphide could be used for conversion into *p*-nitrobenzenesulphenyl chloride of sufficient purity for preparative work, ethereal solutions of the latter were treated with resorcinol. The resulting 4-nitro-2′ : 4′-dihydroxydiphenyl sulphide (I) did not crystallise well, but its m. p. was only slightly lower than that of the pure compound. Oxidation of this impure (I) with perhydrol in acetic acid, which is known (Burton and Hoggarth, *J.*, 1945, 469) to degrade pure (I) to *p*-nitrobenzenesulphonic acid, gave an appreciable amount of a compound, m. p. 252—253°, which from its analysis appeared to be 4 : 4′-dinitrodiphenylsulphone and which undoubtedly arises from 4 : 4′-dinitrodiphenyl sulphide present (see Bennett and Youle, *J.*, 1938, 889) in the original disulphide and (I). This sulphone has been prepared (Fromm and Wittmann, *Ber.*, 1908, **41**, 2269; Waldron and Reid, *J. Amer. Chem. Soc.*, 1923, **45**, 2410) by chromic acid oxidation of the sulphide and is reported in both cases to melt at 282°, but Bennett and Youle (*loc. cit.*) record m. p. 251—254°.

In connection with an investigation which we are carrying out on the synthesis of various pyridylarylsulphones, we found that interaction of *p*-chloronitrobenzene and 4-thiopyridone in alcoholic alkali gave *ca.* 36% (on *p*-chloronitrobenzene used) of 4 : 4′-dinitrodiphenyl sulphide and that further oxidation gave the sulphone, m. p. 252—253°. We have also found that boiling aqueous sodium hydroxide decomposes 4-thiopyridone with the formation of sodium sulphide (coloration with sodium nitroprusside).

The discrepancy in the m. p. of our sulphone led us to prepare it from 4 : 4′-dinitrodiphenyl sulphide which had been made in the laboratories of Imperial Chemical Industries Limited, Dyestuffs Division. Oxidation with perhydrol or chromic acid gave the sulphone, m. p. 252—253°.

All the specimens of sulphone of m. p. 252—253° were reduced to the known 4 : 4′-diaminodiphenylsulphone.

4 : 4′-*Dinitrodiphenylsulphone*.—(i) Crude, finely powdered 4 : 4′-dinitrodiphenyl disulphide (15·4 g.) suspended in dry chloroform (100 c.c.) was treated with a fairly rapid stream of dry chlorine until a clear solution was obtained. The solvent was evaporated in a vacuum and dry ether (75 c.c.) added to the residue, when some material remained undissolved. The filtered, ethereal solution was added to resorcinol (11 g.) in dry ether (75 c.c.) and, after short refluxing, evaporation, and dissolution of the residue in the minimum amount of boiling 50% acetic acid, crude 4-nitro-2′ : 4′-dihydroxydiphenyl sulphide (16·3 g.), m. p. 179—180°, was obtained. Zincke (*Annalen*, 1913, **400**, 26) gives m. p. 182°, whilst Burton and Hoggarth (*loc. cit.*) record 184° for the pure compound. Oxidation of the crude sulphide (10 g.) with perhydrol (50 c.c.) in boiling acetic acid (100 c.c.) gave 2·5 g. of sulphone, m. p. 250°, raised to 252—253° by crystallisation from acetic acid (Found : C, 46·7; H, 2·8. Calc. for $C_{12}H_8O_6N_2S$: C, 46·7; H, 2·6%).

(ii) A mixture of *p*-chloronitrobenzene (6·3 g.), 4-thiopyridone (4·45 g.) (King and Ware, *J.*, 1939, 875), potassium hydroxide (2·25 g.), and alcohol (50 c.c.) was refluxed for 18 hours. Evaporation and addition of water gave a gummy product which gave (from alcohol) 1·9 g. of 4 : 4′-dinitrodiphenyl sulphide, m. p. 156—157° (Found : C, 52·2; H, 3·0; N, 10·15; S, 11·7. Calc. for $C_{12}H_8O_4N_2S$: C, 52·2; H, 2·9; N, 10·2; S, 11·6%). Oxidation with perhydrol (4 mols.) in acetic acid at 100° gave the sulphone, m. p. 252—253°, unaltered by four crystallisations from acetic acid (Found : N, 9·5; S, 10·7. Calc., N, 9·1; S, 10·4%). Authentic 4 : 4′-dinitrodiphenyl sulphide was similarly oxidised, and also as described by Fromm and Wittmann (*loc. cit.*), to the same product, m. p. and mixed m. p. 252—253°.

4 : 4′-*Diaminodiphenylsulphone*.—(i) The dinitrosulphone was reduced with hydrogen in the presence of Raney nickel and methyl alcohol at ordinary temperature and pressure. The solution gave the diaminosulphone, m. p. 178° (from water).

(ii) The dinitrosulphone (7 g.), iron filings (15 g.), alcohol (100 c.c.), water (15 c.c.), and concentrated hydrochloric acid (1 c.c.) were stirred under reflux for 3 hours, made alkaline with ammonia, and filtered hot. The residue from the evaporated filtrate was dissolved in hot dilute hydrochloric acid (charcoal) and the base precipitated by sodium acetate. Recrystallisation from water gave colourless needles, m. p. and mixed m. p. 178° (Found : C, 58·5; H, 4·8; N, 11·2; S, 12·9. Calc. for $C_{12}H_{12}O_2N_2S$: C, 58·1; H, 4·8; N, 11·3; S, 12·9%). The base was further characterised as its diacetyl derivative, m. p. and mixed m. p. 285—286° (Found : N, 8·3; S, 9·5. Calc. for $C_{16}H_{16}O_4N_2S$: N, 8·4; S, 9·6%).

We thank Imperial Chemical Industries Limited for a grant to one of us (W. A. D.) and also for the gift of chemicals.—The University, Leeds, 2. [*Received, January 25th*, 1946.]

PRESIDENTIAL ADDRESS.

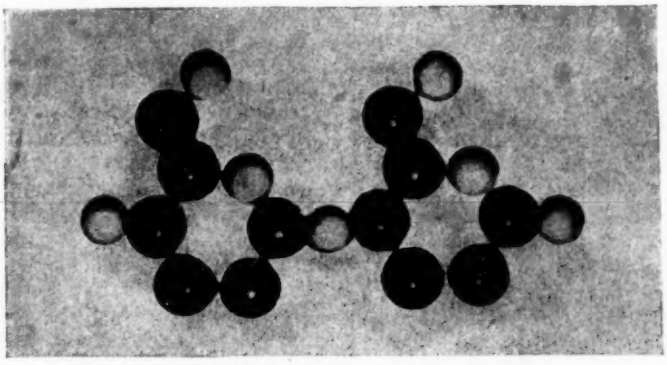
DELIVERED BEFORE THE CHEMICAL SOCIETY ON APRIL 19TH, 1945.

Starch.

By W. N. HAWORTH, D.Sc., F.R.S.

IT is a curious fact that some of the most notable advances in the chemistry of starch have been made during the stress of this and earlier wars: witness the discovery of the iodine coloration by de Claubry (1814); the isolation of glucose from starch in the same year by de Saussure, who also recognised maltose five years later; the detection of sugars in the products of acid hydrolysis in 1811 by the Russian chemist Kirchhoff and his discovery of diastase (β-amylase) about 1815; the separation of amylose and amylopectin in 1915 by Tanret and the purification of the former by adsorption on cellulose. These are all outstanding events in the history of starch. But in the present war we have witnessed the enzymic synthesis in the laboratory of both amylose and amylopectin, which I shall here describe, and the development of facile methods for their recognition and their isolation as two distinctive entities from starch.

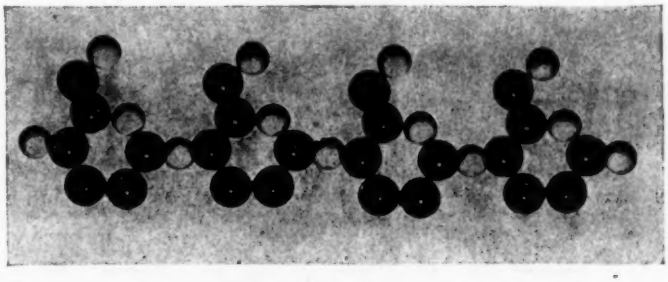
FIG. 1.



In my address today I shall review much of this later development and include in my survey some new researches which have not yet been published. It would perhaps be appropriate on an occasion of this kind to occupy the first few minutes of my address by referring to a few of the fundamental developments which have contributed to our knowledge of the constitution of starch.

We were able in 1927 in my School at Birmingham to establish that the disaccharide maltose, a product of the action of amylases on starch, had the constitution represented, in skeleton form, by Fig. 1, and that starch itself consisted of chains of glucose residues mutually linked, line ahead, by α-1 : 4-glucosidic bonds as shown in Fig. 2. Doubt had been thrown, without real reason, on the view that the maltose

FIG. 2.

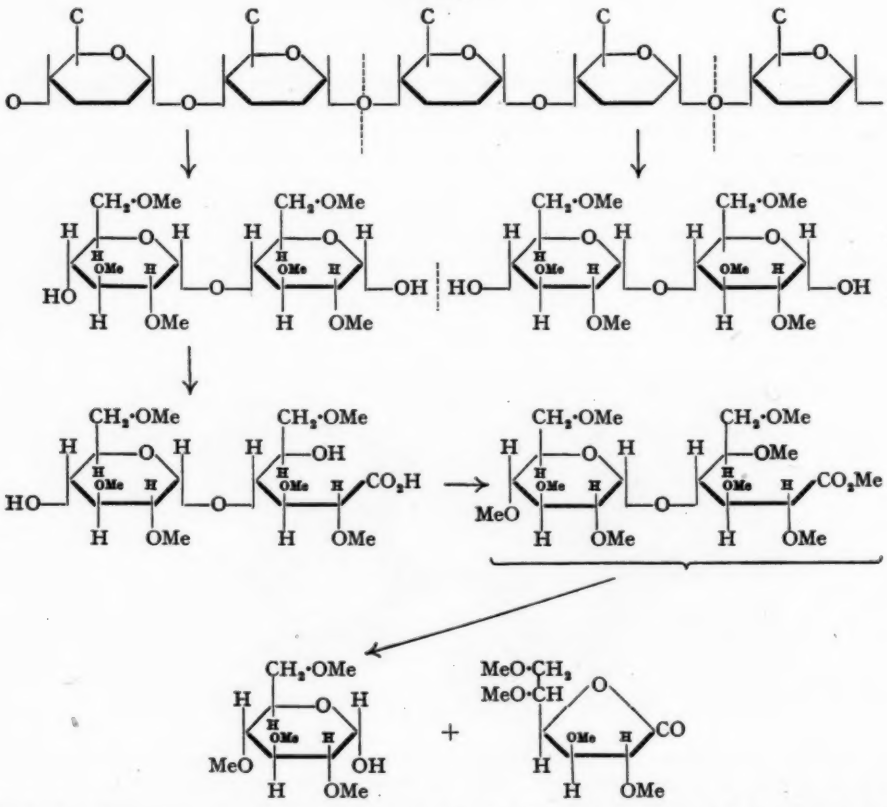


structure was represented in the constitution of starch, the suggestion being that the enzymes present during the breakdown were also capable of uniting two glucose members to give maltose. The implication that maltose units exist preformed in starch was given experimental confirmation in 1930 by Percival and myself (see Fig. 3). We were able to show that methylated starch undergoes scission by acetyl bromide at room temperature to yield products in which the 1 : 4-linkage of maltose survives.

It is of interest to contrast the structures of cellulose and of starch, which differ only in the configuration of the glucosidic bonds. These are α-glucosidic in starch and β-glucosidic in cellulose. I drew attention to this

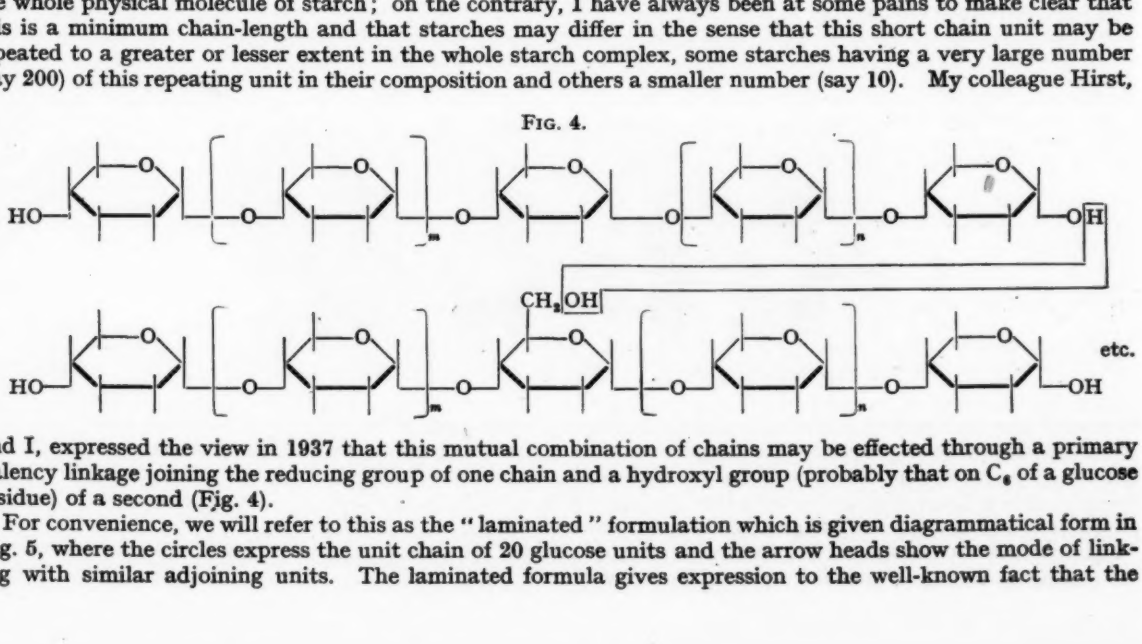
fact in my book in 1929, and indicated that while the β-linkage in cellulose would confer a rectilinear structure on the chains, the starch chains being α-linked would tend to assume a spiral conformation, and this idea has found remarkable confirmation in the views which will be developed later in this address.

FIG. 3.



The method of end-group assay which I developed in the first instance for cellulose and applied to starch in 1932 appeared to show that starch was constituted of short chains of some 24—30 glucose units. As some misapprehension has arisen I wish to repeat here that we have never regarded this short chain as constituting the whole physical molecule of starch; on the contrary, I have always been at some pains to make clear that this is a minimum chain-length and that starches may differ in the sense that this short chain unit may be repeated to a greater or lesser extent in the whole starch complex, some starches having a very large number (say 200) of this repeating unit in their composition and others a smaller number (say 10). My colleague Hirst,

FIG. 4.



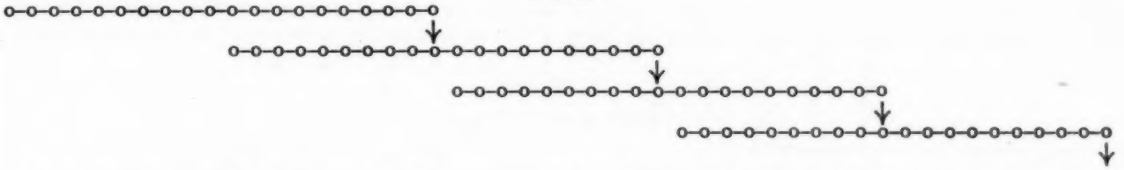
and I, expressed the view in 1937 that this mutual combination of chains may be effected through a primary valency linkage joining the reducing group of one chain and a hydroxyl group (probably that on C_6 of a glucose residue) of a second (Fig. 4).

For convenience, we will refer to this as the "laminated" formulation which is given diagrammatical form in Fig. 5, where the circles express the unit chain of 20 glucose units and the arrow heads show the mode of linking with similar adjoining units. The laminated formula gives expression to the well-known fact that the

molecular weights of starches are many times greater than that of the unit-chain. Direct evidence that the cross-link is indeed a 1 : 6-glucosidic bond and that it probably has the α-configuration was provided subsequently by the work of Hirst, of Freudenberg, and also of Myrbäck who found evidence of an *iso*gentiobiose (Fischer's *iso*maltose) linking in a trisaccharide derived from the enzymic breakdown of starch.

FIG. 5.

Starch.



Up to recent years the balance of evidence appeared to favour the view that native starch, whatever its source, was essentially homogeneous in a chemical, but not a physical, sense. From the days of Maquenne's classical work at the beginning of the century it has been recognised that starch contains at least two components which differ markedly in their physical properties and in respect of the action of amylases upon them; very many methods for effecting the separation of these components, which were named amylose and amylopectin by Maquenne, have been proposed, but all of these methods are not equally efficacious. It is indeed due to the inadequacy of many of the procedures which were described that the recognition of amylose and amylopectin as distinct chemical species has been so long delayed.

It is interesting to find that only three of the older methods proposed do in fact achieve a separation of two chemically distinct entities from starch and that two of these methods originated with Tanret in 1915. One of these, the leaching out of the amylose component with hot water, was greatly improved and developed by M. E. Baldwin in 1930 and applied in 1940 by K. H. Meyer, who obtained in this way a fairly pure amylose, albeit in poor yield, from corn and potato starches. This amylose was shown by Meyer to be constituted not of branched but of long unbranched chains, as we have likewise found to be the case in the synthetic polysaccharide of Hanes.

A better method of separation was provided by Schoch in 1941. This method consists essentially in the heating of a starch paste in an autoclave at 120° with butyl or amyl alcohol whereby the amylose component is precipitated; the amylopectin is separated from the mother liquor by the addition of ethyl alcohol. The weight yield of amylose in several runs was 25% of corn starch. A comparison of the properties of amylose and amylopectin is shown in the table below.

Comparison of Potato Amylose and Amylopectin.

	Amylose.	*Amylopectin.*
Iodine colouration.	Intense blue.	Red-brown.
Blue value (Spekker absorptiometer).	1·35	0·05
β-Amylase action.	Completely converted to maltose.	50% conversion to maltose. Residue of limit-dextrin-A.
Solubility in water.	Sparingly soluble.	Very soluble.
Solubility in ethylenediamine hydrate.	Readily soluble.	Sparingly soluble.
Stability in aqueous solutions.	Undergoes spontaneous precipitation (retrogradation).	Stable indefinitely (no retrogradation).
Intrinsic viscosity in ethylenediamine solution (c in g., %).	1·15 (from arrowroot starch)	0·4 (from arrowroot starch)
End-group assay.	100 or more glucose members.	Repeating unit chains each of about 20 glucose members.
X-Ray diagram.	V-pattern (for alcohol-precipitated amylose).	Amorphous.
	Amylose acetate.	*Amylopectin acetate.*
Form.	Fibrous; forms tough films and fibres.	Amorphous powder; forms brittle films; cannot be spun.
Viscosity (in chloroform): Intrinsic viscosity (c in g., %)	2·45	1·08
$\eta_{sp.}/c$	Increases with concentration.	Independent of concentration.
Molecular size.	Comparatively low.	Very high.

Of these properties, the most easily recognisable are the colours given by iodine and the relative completeness of hydrolysis by β-amylase.

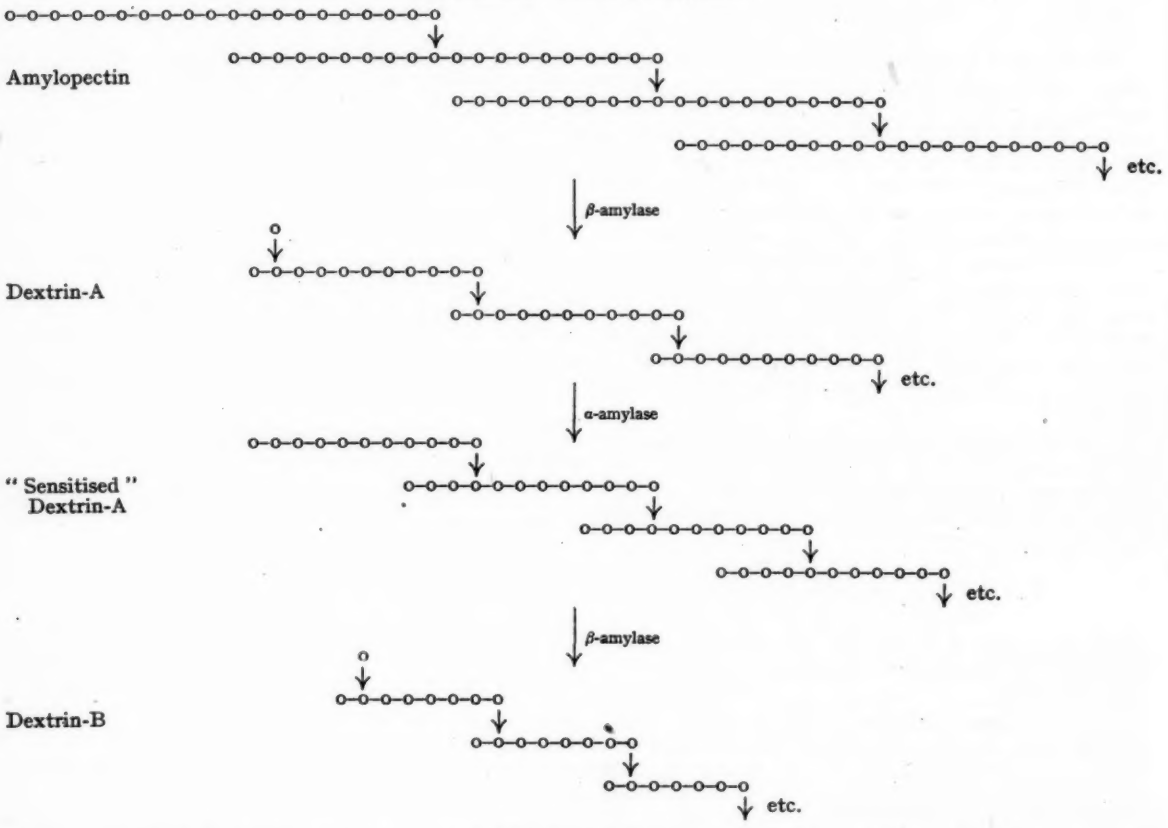
We have been able very recently to develop a new method of separation which yields relatively pure specimens of amylose and particularly of amylopectin from potato starch. This consists, briefly, in saturating a starch paste with thymol at 20—30° while keeping the solution at room temperature for 2—3 days; thymol is very sparingly soluble so that very little is needed. The amylose is thus precipitated and the remaining amylopectin still contains a little amylose which can be removed by saturating an aqueous solution of the amylopectin with *cyclo*hexanol, thus throwing out the residual amylose together with some of the amylopectin.

The amylopectin remaining in solution gives a reddish colour with iodine, whereas amylose gives a pure blue. Other methods of separation are under investigation and with one of these we seem to have achieved the isolation of two very pure components. The intensity of the blue colour given to amylose by iodine is here made the basis for the quantitative analysis of mixtures of amylose and amylopectin. The colour intensity is measured by the method of Hassid and McCready using a Spekker absorptiometer.

The difference in the action of β-amylase on the two components of starch is very marked. Amylose, constituting 20—25% of starch, is converted completely to maltose, whereas the amylopectin is converted to maltose to the extent of 50% only, the residue being a red-staining dextrin (dextrin-A) which resists the further action of β-amylase. We have postulated as the cause of this resistance the presence of the α-linking shown by

FIG. 6.

Degradation of starch by amylases.



the arrow in the formulation of amylopectin in Fig. 6, and the position of this linking may be determined by the extent to which maltose members are released from the left-hand side of the chains shown in this formula for amylopectin. In earlier work (Haworth, Kitchen, and Peat) we have shown that this resistance to β-amylase is overcome in dextrin-A by momentary contact with α-amylase. This may be due to the severance of this α-linking by the α-amylase and the recombination, possibly owing to the presence of a Q-factor in the α-amylase, of the shortened unit chains by the reconstruction of this α-linking in another position. Certainly it is the case that the " sensitised " dextrin-A is now capable of further attack by β-amylase to give maltose and a new dextrin-B as indicated by the lower formulation in Fig. 6.

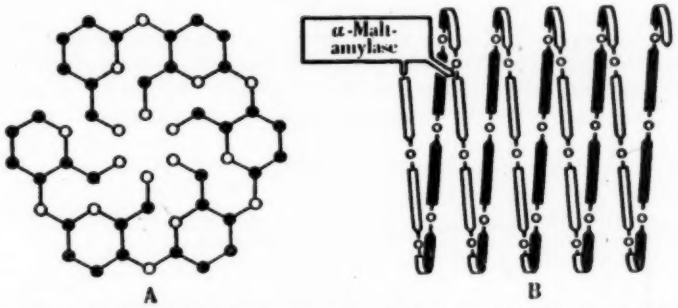
Natural amylose and amylopectin are chemically different in the sense that amylose is composed of largely unbranched chains of 100 or more glucose members whereas amylopectin is given a laminated or branched structure composed of unit chains of about 20 glucose residues.

Amylose has been obtained in crystalline form. This was achieved by Kerr and Severson who used for its separation a combination of the leaching out method of Tanret and the method of Schoch. *X*-Ray examination of this crystalline amylose by Rundle led him to support a helical structure for amylose and for the amylose–iodine complex. The molecular structure suggested is shown in Fig. 7, and is here reproduced from the paper by C. S. Hanes, together with his subscript, in " The New Phytologist " (1937, **36**, 101).

Each turn of the spiral is made up of six glucose residues and a molecule of iodine is neatly accommodated in each turn, this forming the intensely coloured amylose–iodine complex. This helix theory is, of course, not

new. I had proposed it on geometrical grounds in 1929 and later Hanes adopted the idea to explain the mode of action of α-amylase (see Fig. 7). It is perhaps worthy of remark here that an amylose solution, when free from amylopectin, is colloidally unstable, and that amylose is closely related in properties to cellulose. In particular, amylose acetate, which is fibrous in appearance and indistinguishable by eye from cellulose acetate, forms tough clear films which, when formed under tension, give *X*-ray fibre diagrams of the cellulose type (Whistler). It is possible that in these stretched films the amylose acetate is in an extended, and not in a helical, form.

FIG. 7.

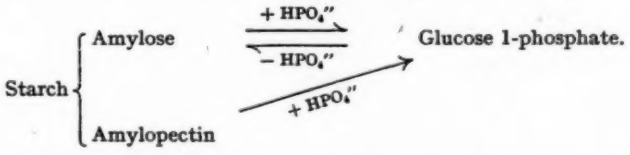


A, *hexagonal arrangement of* 6α*-linked glucopyranose units* (*Sachse conformation*) *modified after Haworth* (1929). B, *hypothetical spiral model of* α*-linked chain of* 30 *glucose units, showing possible mode of combination with* α*-malt-amylase.*

We now come to the important question of the synthesis of starch in the plant. The illuminating researches of C. S. Hanes at the Low Temperature Research Station, Cambridge, ran parallel with the investigations of Cori on the synthesis of glycogen in muscle and it was found that the enzymes concerned in each case used the same substrate, namely glucose 1-phosphate. In 1940, Hanes announced the synthesis *in vitro* of a starch-like polysaccharide from glucose 1-phosphate by the agency of an enzyme, phosphorylase, present in the pea and the potato. In collaboration with Dr. Hanes, we examined this synthetic product and confirmed his impression that it was not identical with natural starch but was rather the amylose component of starch. In other words, phosphorylase effected the synthesis of long, largely unbranched chains of glucose units according to the scheme illustrated in Fig. 8, which we have modified from Hanes's original scheme to be more in keeping with the latest advances.

FIG. 8.

Breakdown of starch and synthesis of amylose by phosphorylase.
(*C. S. Hanes.*)



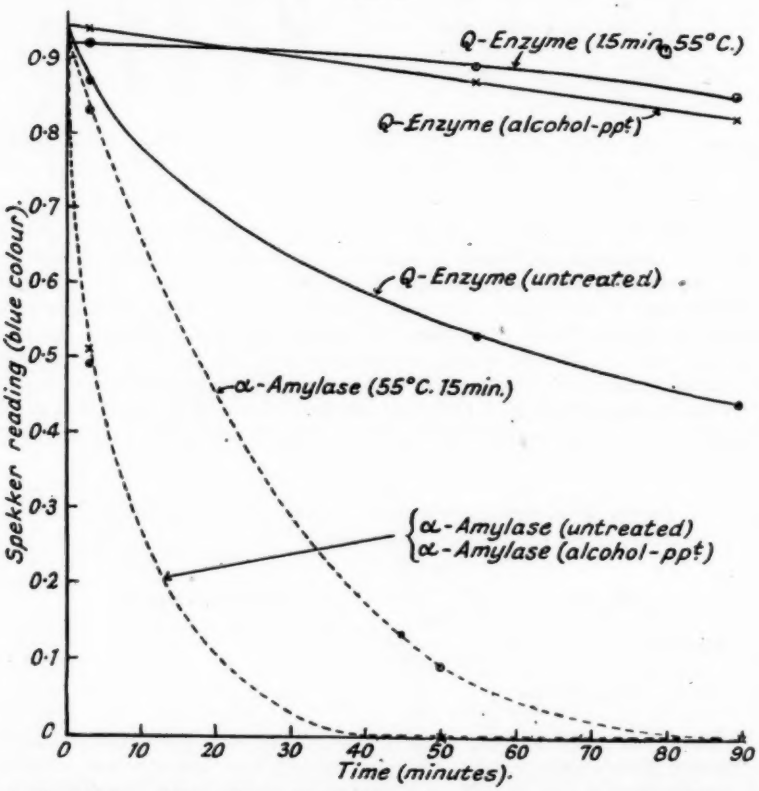
We could not fail to note that only one component of starch, and moreover only that occurring in the smaller proportion, was synthesised by phosphorylase. By what agency was amylopectin, representing about three-fourths of the starch, synthesised in the plant? Clearly phosphorylase represented only a part of the enzyme system concerned with the metabolism of starch, and my colleagues Bourne and Peat therefore made a search for some other factor or factors involved in starch synthesis. They succeeded ultimately in demonstrating the presence of another such agent in potato juice. They established that this new factor was an enzyme, since its activity was destroyed when it was heated to 100°, and I refer to it as the Q-enzyme to distinguish it from the phosphorylase (P-enzyme) with which it is associated. The P-enzyme has now been isolated as a dry powder, apparently stable; the Q-enzyme has been separated from it, but has not yet been obtained in such a state of purity that one can be sure of the complete absence of P-enzyme from the preparation.

With this reservation in mind, I will outline the properties and probable functions of this new factor. The Q-enzyme *per se* appears to have no synthetic function with respect to glucose 1-phosphate. It acts upon starch, however, very definitely as a hydrolytic enzyme, in other words as an amylase. We have satisfied ourselves, however, that it is an amylase of a special type, hitherto unrecognised, and cannot be classified simply as an α- or a β-amylase. The β-amylase of soya bean acting on an amylose separated by thymol produces the immediate liberation of maltose and this reaction proceeds smoothly until the whole of the amylose has been converted into maltose. This observation is in conformity with the view, held generally, that β-amylase makes an endwise attack on the amylose chain and reduces its length by two glucose units at a time. During the course of the reaction the blue colour given by the amylose with iodine becomes less and less intense until ultimately no colour is given. The action of Q-enzyme on amylose is very different. The colour with iodine

slowly changes from blue to a red which thereafter persists, *i.e.*, an achroic point is never reached. The most striking difference, however, lies in the fact that with many preparations of Q-enzyme no reducing power develops during the whole of the time of reaction with amylose; hydrolysis by Q-enzyme evidently does not involve the liberation of a simple sugar. With some preparations of Q-enzyme we have found that sugar production occurs in the later stages of the reaction, but the amount is always very much less than that liberated by an equivalent concentration of α- or β-amylase at the same stage in the reaction. We attribute this occasional production of sugar by Q-enzyme to the presence in the preparations of the latter of an α- or β-amylase. It is known that the potato often contains amylase and we have found this to be especially true of potatoes which are sprouting.

The curves of hydrolysis with Q-enzyme are nearer in type to those of α-amylase than to those of β-amylase. Nevertheless, Bourne and Peat have been able to show that Q-enzyme is not necessarily identical with α-amylase inasmuch as Q-enzyme is inactivated by either heating for a short time at 55° or precipitation from aqueous solution with alcohol. The activity of the α-amylase of saliva is practically unaffected by either of these

FIG. 9.



Comparison of the actions of treated Q- and α-amylase enzymes on amylose.

treatments (Fig. 9). It is to be observed that at this stage no means is available for a comparison of the stability of the enzymes at identical concentrations, since their absolute activities cannot be determined.

I have said that Q-enzyme is not to be regarded as an enzyme capable in itself of synthesising starch from glucose or maltose or glucose 1-phosphate, but, given a suitable substrate, it immediately displays synthetic powers. That substrate is provided through the agency of P-enzyme acting on glucose 1-phosphate, and most probably also by the hydrolytic action of Q-enzyme itself acting upon amylose (and possibly upon amylopectin). We put forward this latter hypothesis, tentatively and with caution, as being the only one which covers the observations that have so far been made. As a working hypothesis, then, we picture the biological synthesis and degradation of whole starch as proceeding according to the scheme shown in Figs. 10 and 11.

This conception of the course of starch metabolism in the potato postulates the formation of an intermediate polysaccharide of unique constitution. This is described in Fig. 10 as " 20 unit-chain (unbranched) " and is to be pictured as composed of single unbranched chains of about 20 glucose units mutually linked by 1 : 4-α-glucosidic bonds. This intermediate product (pseudo-amylose) may be derived (i) from glucose 1-phosphate by the agency of P-enzyme; (ii) from amylose by the hydrolytic action of Q-enzyme; and possibly (iii) from amylopectin in the presence of Q-enzyme. We regard this pseudo-amylose as the only substrate on which Q-enzyme can act synthetically, whereby 1 : 6-cross-linkages are established and amylopectin is formed. The suggestion

is thus made that, when pure Q-enzyme acts on amylose, this long unbranched chain compound is split up into shorter chains (pseudo-amylose) which are then combined laterally with the production of amylopectin. The hypothesis that amylose is converted by Q-enzyme into amylopectin still awaits experimental confirmation.

The conversion of glucose 1-phosphate into amylose by the agency of purified P-enzyme, accomplished in the first place by Hanes, is now to be regarded as taking place through the intermediate formation of pseudo-mylose. In the absence of Q-enzyme, the normal synthetic activity of the P-enzyme does not cease with the production of 20-unit chains but continues until the long, largely unbranched chains of amylose itself are built up. If, however, the P- and Q-enzymes are functioning together in a suitable ratio, the P-enzyme can carry the synthesis only to the stage of pseudo-amylose which thereafter becomes the substrate for Q-enzyme and is converted into amylopectin.

Bourne and Peat have isolated the polysaccharide produced by the completed action of a mixture of P- and Q-enzymes on glucose 1-phosphate; they have shown that it has the characteristics of an amylopectin, having

FIG. 10.

Suggested scheme for synthesis and breakdown of amylopectin and amylose by P- and Q-enzymes of potato.

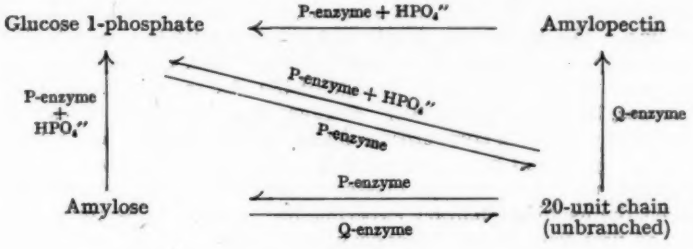
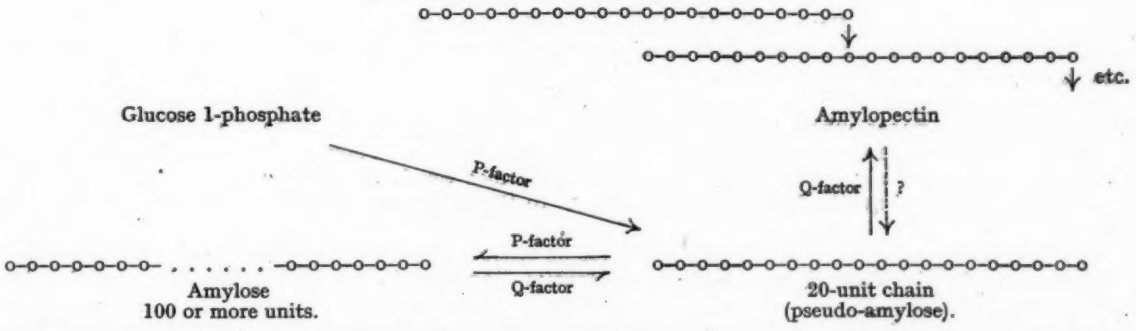


FIG. 11.

Synthesis of amylopectin and amylose.



a branched structure, and by end-group assay have estimated that the repeating chain unit contains an average of 20 glucose members. Incidentally, it is for this reason that we describe pseudo-amylose as being constituted of 20-unit chains.

Fig. 11 also illustrates the katabolic activity of P- and Q-enzymes. Hanes has shown that whole starch is convertible into glucose 1-phosphate by phosphorylase so it must be assumed that the amylose and amylopectin components are both suitable substrates for this enzyme in the presence of phosphate ions. Q-Enzyme, on the other hand, appears to have no phosphorylytic activity. It may be that its hydrolytic activity is confined to amylose as substrate, but it may later appear that amylopectin also forms a suitable substrate for Q-conversion into pseudo-amylose. It would indeed be somewhat remarkable if the synthesis of 1 : 6-links by Q-enzyme were not a reversible reaction.

Much remains to be done. Our hypothesis of the mechanism of starch metabolism is only speculative at present, not because it cannot accommodate all the known facts but because all the knowledge required to substantiate it is not yet available.

OBITUARY NOTICES.

SIR MARTIN ONSLOW FORSTER.*

1872—1945.

MARTIN ONSLOW FORSTER was born in South London on November 8th, 1872; he died in Mysore City on May 24th, 1945, in his 73rd year. He was the fourth and youngest child of Martin Forster (d. 1908) and Anne Hope Limby (d. 1916). An elder brother died in infancy. His paternal grandfather was a lawyer who died young, so that his father, then at Merchant Taylors' School, was orphaned at 16. He became a clerk in the Bank of England and remained there till he retired in 1894, having reached the status of Principal of the Bill Office.

Onslow has described his parents as typical Victorians, kindly, conscientious, prudent and old-fashioned, with strong religious feeling. The home was simple and sedate whilst the parents, like many others in those mid-Victorian days, exercised many economies for the benefit of their children.

Onslow was never a very robust boy and at the age of ten, for reasons of health, he was sent to Margate to school at Dane Hill House, known as Boulden's. Margate was then in the heyday of its fame as a place for preparatory schools and there was much competition among them at cricket and football. Onslow did well in taking prizes; but the most significant happening during his six years there was the formation of a chemistry class under H. T. B. Hodges, one of the assistant masters. The boys were provided with Barff's " Chemistry " and periodically witnessed the usual elementary experiments. Later, on Saturday afternoons he was sent to learn chemical analysis, at first from a Mr. Woodcock, and later to G. R. Tweedie, who introduced him to Valentin's " Qualitative Analysis." The early bias to chemistry was encouraged by a gift of a box of simple apparatus from a cousin which made experiments at home possible.

And so we find him in October 1888 entered at Finsbury, apparently on the advice of Mr. Dreaper, the father of W. P. Dreaper who, after finishing the course there, had just been appointed Chemist to Courtauld's silk-crape dyeing works at Braintree. He thus came under the influence of Castell-Evans and F. W. Streatfeild, teachers to whom so many chemists have paid tribute. Forster has written of the state of chemistry in these days in his 20th Streatfeild Memorial Lecture delivered to the Institute of Chemistry. He gained the Certificate after 2 years, being bracketed first, and spent a further year in Meldola's private research laboratory, his name being on a paper published by Meldola in 1891—" Researches in the triazine series."

Forster's wish was to enter industry as G. T. Morgan and others were doing, but his father felt that further training was desirable in spite of the serious monetary sacrifice which would be involved. He sought advice from many people and finally decided to send Onslow to Würzburg where Emil Fischer was making a great reputation.

It should be remarked that at this date there was no school of chemistry at either Oxford or Cambridge at all commensurate with their dignity as great Universities. Another factor was the necessity to a chemist of knowing German thoroughly.

Forster went to Würzburg in September 1891 where, after a short course of organic preparations, he was given the task of elucidating the structure of a hydroquinoline base produced when methylketole is heated with methyl iodide in sealed tubes. The work proved too difficult and after many months of unsuccessful experiments Fischer transferred him to a simple " Doctor-Arbeit " involving the condensation of methylketole with aldehydes and ketones. Fischer had by this time received the call to the Professorship at Berlin consequent on the death of Hofmann, so examination dates were advanced and Forster took his Ph.D. (*magna cum laude*) in July 1892.

The social and student life at Würzburg, with its free and easy customs, was a great awakening to Forster after the sedate atmosphere of Clapham and Finsbury. Here he met as fellow student Arthur W. Crossley and founded a life-long friendship which was to influence both men greatly. Life in the smaller German university towns in those days was cheap and convivial; the students played and worked hard and took readily to foreigners in spite of linguistic shortcomings. The material resources of the laboratory were little different from those at Finsbury, but for the first time he met a galvanic personality in Emil Fischer, then thirty-nine. Fischer at that time, as later in Berlin, visited and spoke to every student twice a day however unimportant their themes were and so impressed on them something of his enthusiasm and vitality. He was then at one of the most exciting stages of his sugar work and the atmosphere in the laboratory must have been tense. One of the writers had the same experience in Berlin eight years later when unswerving singleness of purpose was still Fischer's salient quality in life: he lived for his research work. Forster, Crossley, and those others who were privileged to work with him were infected and have retained for life that burning desire to add to knowledge by working at the bench.

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M. O. Forsler.

[*To face p.* 550

" For giving me desire
An eager thirst, a burning ardent flame
That did incessantly a Paradise
unknown suggest and something undescribed
discern, and bear me to it; be
Thy name for ever praised by me."

TRAHERNE

Forster's debt to Fischer was in some measure repaid by the brilliant memorial lecture which he delivered to the Chemical Society in October 1920. He also paid homage to his teacher by his presence at the sixtieth birthday celebration in Berlin, which was by Fischer's desire an almost domestic affair.

On his return from Germany, after a few weeks in Meldola's laboratory, Forster went to Mason College, Birmingham, as private assistant to Professor W. A. Tilden. He remained there for nearly two years until July 1894. He speaks of the association as being a most happy and fortunate one; Tilden was not only kind at the time but consistently furthered his progress on subsequent occasions. Forster was fortunate in that he was stimulated by three such leaders as Fischer, Tilden, and Armstrong: as a consequence the love of work at the laboratory bench remained his dominant passion in life.

Here Onslow made friends with Sidney Williamson and J. H. Miller, also Emil Hatschek. He had a great capacity for life-long friendship with those he liked; to others he was distant and aloof, and in later years he had an air of superiority which did not make him generally popular. From Finsbury days he had liked Julian L. Baker—later he formed the closest association with G. T. Moody and W. J. Pope at the Central, also with G. T. Morgan whom he had first known at Finsbury but became specially intimate with when at the Royal College of Science. Those named, with A. W. Crossley, formed a closely knit band of friends able to help each other materially, and collectively to exert considerable influence in chemical, especially Chemical Society, circles.

At Birmingham Forster became practised in the art of making nitrosyl chloride and isoprene: he writes in his Streatfeild lecture how he sought occasional inspiration by respectfully gazing at a small bottle of colourless fluid submerging a sticky solid—the first ounce of rubber produced independently of the plant. He adds that it is true this transformation was never properly explained.

At this stage of his career Forster abandoned the idea of going into industry and realised that if he drifted into teaching he would require a London degree. Tilden had at this time transferred to the Royal College of Science in succession to T. E. Thorpe, who had gone to the Government Laboratory, and as Tilden could not find a place for him there Forster entered at the Central Technical College as a research student under H. E. Armstrong.

Thus in October, 1894, he first came to know Armstrong and the band of workers around him in an atmosphere of scientific endeavour which closely resembled that created by Emil Fischer. Forster found Armstrong most stimulating—he was set to work on camphor, then the chief subject of the laboratory research, undertaking in particular the study of the action of fuming nitric acid on camphor. Henceforth Forster, as we shall describe later, made camphor chemistry the chief study of his life.

At Christmas 1894 Forster was awarded the first Salters' Company's Research Fellowship of £150 a year at the Central. This was the first of this type of research fellowship; it was duplicated by the Leathersellers' Company and was due to Armstrong's representations to his life-long friends in these two great guilds. Few fellowships have been more productive of results—all the recipients have done most distinguished work largely in British industry, where they have attained the highest positions.

But Forster only held his Fellowship for a year, instead of the three years possible, being tempted by an offer from Tilden of a vacant junior demonstratorship at £100 per annum at the Royal College of Science. This was naturally against Armstrong's advice, who saw a much more brilliant career for Forster.

Christmas, 1895, began an association with the Royal College of Science which lasted for eighteen years until 1913, a period of outstanding scientific activity which placed him in the front rank of British organic chemists. At first he worked under J. W. Rodger, succeeding him as Senior Demonstrator in the South Laboratory on his death in 1897—Morgan then took Forster's place and the two collaborated, though not in research work, in greatest harmony until 1910.

Onslow owed much to the training of W. P. Wynne, a great believer in detail and accuracy and one of the neatest of manipulators, whom he succeeded as Assistant Professor in 1902.

Meantime Forster had overcome the various hurdles leading to the London Doctorate, which he took at the same time as Morgan in 1899 when he was awarded the Granville prize for his thesis.

The promotion to what was virtually a professorship in organic chemistry gave much greater facilities for research, including space, time, and help from advanced students. Forster was particularly fortunate in attracting a very brilliant Swiss—H. E. Fierz, who remained with him for four years. The association was a happy and valuable factor in the life of both; they published much first class work together; it led also to eight more Swiss coming to work under Forster. He had also a long list of English associates whose names are to be found on the published list of their joint papers.

The period 1902—1913 saw a broadening in Forster's activities. He was elected to the Royal Society in 1905 at the unusually early age of thirty-three and began to take a leading position in the administration of

the scientific societies. He did much for the Chemical Society; elected a Fellow in 1892 he spoke often at the meetings of which he was a most regular attendant. Almost all his papers were contributed to it and they are notable for the clarity and brilliance of their exposition. This latter quality was not confined to the written word since it was generally regarded as a " field-day " when Forster read a paper at one of the meetings of the Society. After serving on the Council 1901—1904 he was Honorary Secretary during 1904—1910, Treasurer 1913—1933, and Vice-President 1910—1913. In 1918 the Society awarded him its highest distinction, the Longstaff Medal.

In 1905 the Annual Meeting of the Society of Chemical Industry took place in London under the presidency of Dr. William H. Nichols, a successful leader of chemical industry in the United States. His supporters included his wife and daughter Madeleine whom Onslow married in New York on January 1st, 1907. After this, Forster went every year to America, spending the summer at their summer home in the Thousand Islands, St. Lawrence River. For several years the marriage was a happy one but estrangement gradually became increasingly acute and the final disruption occurred in September, 1916. This was an overwhelming disaster for Onslow and one which had its effect for some years on his career.

In 1905 also Forster went to South Africa with the British Association, acting as one of the secretaries of the Chemistry Section. He was President of the Section at the Edinburgh meeting in 1921 where he delivered a brilliant address.

The future for a great school of organic chemistry at the Royal College seemed rosy, but there were clouds in the sky. Tilden retired in 1909 and Thorpe, now Sir Edward, came back as professor. He showed no sympathy towards the organic chemistry school, prescribing, for example, nine preparations as enough for the final course as compared with forty required by Fischer. Matters became even worse when H. B. Baker succeeded Thorpe for he had even less regard for Forster's subject. Morgan had gone to Dublin so Forster had to fight alone. The organic school at the Central had also been shut down when the City Guilds College was absorbed by the Imperial College. Forster resigned, a disappointed man, turning his attention for a change to politics, hoping, if elected, to represent science in Parliament and fight for its recognition. He was adopted prospective Conservative candidate at Blackburn and nursed the constituency for three years taking an energetic interest in the work.

In 1914 came the war and Forster like many others tried to get something useful to do. The dye-using industry was in chaos for they had insisted on purchasing all their dyes abroad and found their supplies cut off. In the spring of 1915 Mr. James Falconer, who had been charged by the Government with the Chairmanship of British Dyes Ltd., offered Forster the Chairmanship of the Technical Committee of the Company which had purchased the Huddersfield dyestuffs factory of Read Holliday and Sons. He became a Director in 1916.

Few subjects have aroused greater controversy and personal disagreements than the conduct of the dyestuff industry at this period, so that it is preferable to avoid it here. Forster and his colleagues resigned in 1918. His activities were not confined to the technical side of the industry: he was mindful of the importance of social amenities for the staff, being responsible for the first staff club at Huddersfield.

During 1918 the Worshipful Company of Salters had discussed the idea of directing part of their income to the encouragement of chemistry and its application to industry. Their plans matured and in December 1918 Forster was appointed Director of the Salters' Institute of Industrial Chemistry with an office attached to the Company's hall in St. Swithin's Lane. Here a large number of young ex-officers and others, whose chemistry training had been interrupted by the war and who desired to resume it, assisted by Salters' Fellowships, were interviewed. Meanwhile Forster, assisted by W. B. Saville, retained a place at the Davy–Faraday Laboratory, where he continued his research work choosing as subject the constitution of picrorocellin. The original appointment by the Salters' Company had contemplated the construction of laboratories, but it became clear after 3 years that the rebuilding scheme would not take shape. So Forster agreed to a reduced salary so as to have his afternoons free for the laboratory in Albemarle Street.

It is opportune to praise here the enterprise of the Salters' Company not only in giving many young men the chance to complete their training in some degree of financial comfort but also in engaging the help of leaders of experience to advise them in their enlightened tasks. Forster's experience both as a teacher and in industry undoubtedly proved of the greatest value. He was followed, as is well known, first by Professor Smithells and later by Sir Robert Robertson.

Forster's father was a dyer, and Onslow became a Liveryman of the Guild in 1894. He reached the Court in 1913, was Renter Warden in 1918—1919 and Prime Warden in 1919—1920. As Renter Warden he was instrumental in adding to the Livery twenty new members distinguished in the dyeing and dye-making industries; until then he had been the only member of the Company even remotely connected with the craft it represents.

Addison desired his readers to consider the world in its most agreeable aspects. In many respects this was Forster's attitude. Tall and good looking, surrounded by influential friends, life was easy for him for many years. His working bench was his first loyalty; he largely controlled the Chemical Society for many years and gave a helping hand to the other chemical societies—he was one of the founders of that much-needed body, the Association of British Chemical Manufacturers, at the end of the last war, which has since played so prominent a part in the establishment of a powerful and progressive chemical industry in this country.

In his few general addresses he shows an assurance of the fact that we discover the perplexities of the world and propound the problems only to find that we must ourselves supply the answers. Yet in general he was not prepared to break a lance for progress notwithstanding his professed parliamentary aspirations. Forster did his best work in his Indian phase, which we are about to chronicle—in England he failed to become the leader which he might have been expected to be with the unusual opportunities vouchsafed him. His own early years were drab enough and attended with sufficient severity of circumstance to elicit his latent powers.

Some account must now be given of the great service which Forster, as Director of the Indian Institute of Science, was able to render to the development of scientific research in India. But first it is necessary to recount briefly the history of this Institute. It owes its origin to the foresight and munificence of Mr. J. N. Tata, a Bombay industrialist who in 1896 offered to endow a trust with Rs. 30 lakhs for the encouragement of research in India. At this time the teachers in the Indian universities, which were modelled on the University of London, had, with a few notable exceptions, done little to advance knowledge. Mr. Tata recognised that if India was to attain a position worthy of her past this must be based on research. After taking the advice of Sir William Ramsay, Sir David Orme Masson, and Colonel Clibborn, it was decided to build a Research Institute on a site made available by the Government of Mysore some three miles from the outskirts of Bangalore. Mr. Tata did not live to see his plans come to fruition, but his sons, Sir Dorabji and Sir Ruttonji Tata, gave full effect to his wishes. In 1906, on the recommendation of the Royal Society, Dr. M. W. Travers was appointed the first Director and he designed the fine buildings which now house the Institute. The first students were admitted to the Departments of General Chemistry, Applied Chemistry, and Electrical Technology in July 1911, the Organic Chemistry Department being opened in September of that year. The intention of the founder was that the Institute should not only impart advanced knowledge and instruction in the methods of research but that it should also assist in the development of Indian industry.

Unfortunately the early days of the Institute were not free from controversy and in 1914 Dr. Travers resigned. The outbreak of the 1914—1918 war naturally interfered with the appointment of a new Director from England and Sir Alfred Bourne, a distinguished biologist, who had retired recently from the position of Director of Public Instruction in Madras, consented to fill the vacancy. This position he held until 1921 when the Visitor, the Viceroy, prior to filling the vacancy appointed a committee of enquiry, with the late Sir William Pope as chairman, to report on the working of the Institute. In their report the committee, in addition to proposing new regulations and by-laws, recommended that the new Director should be a " scientific man of eminence and of proved administrative ability . . . steeped in scientific modes of thought and scientific aspirations."

It was natural that Pope, who was consulted on the appointment of the new Director, should find just these qualities in his friend of the Central days who had in addition a fine presence and the requisite social qualities. Forster's acceptance, at the time of his 50th birthday, involved no small personal sacrifice. It meant the cessation of his work at the laboratory bench and the severance of the close ties which bound him to the scientific life of the metropolis. He recognised, however, that it offered him the opportunity of serving science in a different manner and history may well think that the eleven years during which he was Director enabled him to make his most lasting contribution to science. He had been warned that his reception might not be too cordial and in fact certain members of the staff were hostile to his appointment. One organ of the Press called him " a white elephant." As those who knew Forster had anticipated, he rapidly reached the most cordial relations not only with the staff but, what was of even greater importance, with the students. He was able through the generosity of Sir Dorabji Tata to build for them a spacious club house with a billiards table, library, and indoor games, whilst six tennis courts and a cricket field provided facilities for outdoor recreation. He himself made full use of the club; he played tennis there regularly and on two occasions he won the billiards handicap. In his own home the students were always welcome and he entered very fully into their life. The amicable relations established between the staff and students had their natural outcome in the high standard of research carried out in the laboratories so that competition for admission then became keen. The great contribution which the Institute has been able to make to the world war effort shows that the tradition has been maintained and this was a source of much satisfaction to Forster.

In the first few years after his appointment he continued to supervise the work of a few research students but later, under the burden of his administrative duties and owing probably also to the somewhat enervating climate of Bangalore, he left this to the head of the organic chemistry department. His keen interest in original work remained undiminished and he never failed to attend the meetings of the colloquia where his sage council was much appreciated. He also edited the Journal of the Institute.

When Forster first went to Bangalore he found there the following Professors: J. J. Sudborough (Organic Chemistry), G. J. Fowler (Biochemistry), H. E. Watson (Inorganic Chemistry), and Alfred Hay (Electrical technology). Professor J. K. Catterson Smith replaced Hay in 1923, R. V. Norris came instead of Fowler in 1924, whilst J. L. Simonsen followed Sudborough in 1925. When in 1927 a lecturer was appointed to each of the four departments promising young Indians were appointed in each instance. The team was a first-class one: it enabled Forster to give an increasing amount of his time to administrative and social matters and so further the prestige of science in India.

In December 1925 Onslow married again, to Mrs. Elena Hayes Parodi, widow of a barrister of Gibraltar, whom he had first met in Granada during a visit to Spain with G. T. Morgan in 1901. Her first husband died in 1922 and she spent three years in California until she joined Onslow in India.

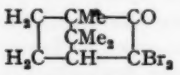
Forster took the opportunity of the annnal meetings of the Indian Science Congress to visit various parts of India and he was President of the Benares meeting in 1925. To these meetings he had always something of value to contribute and few who were fortunate enough to attend the Lahore meeting in 1926 will forget the speech which he made at the annual dinner.

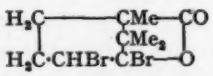
Forster should have retired in 1927 but at his own request he was re-appointed for a further three years when he was asked by the Council to continue for a further period of two years, finally retiring in March 1933. In conferring a knighthood when he retired, the Governmant of India not only honoured him but themselves. On his retirement, guided by his wife's wish for sunshine, he went to live in Mysore City in a house which had been placed at his disposal by the Maharajah of Mysore and which the industry and imagination of his wife and step-daughter Carmen converted into a picturesque and comfortable home. Deeply attached as Forster was to India—in one of his last letters he referred to it as " this dear old country "—there is little doubt that he himself would have preferred to have returned to England. Lady Forster wished, however, to remain in India and they only paid occasional visits to the home country, the last being in 1939. After Lady Forster's death in 1941 his life was somewhat lonely, brightened only by visits from his step-daughter Carmen who had married Sir Donald Field, and their young son, and by Forster's adopted son, Francis, a Flying Officer stationed in Ceylon. To the end he continued to follow the advancement of science and a reprint of his last article in *Current Topics*, a eulogistic review of Professor A. V. Hill's report on his Indian visit, reached this country shortly after his death. He had made preparations to return to England when the conditions of travel permitted, but his sudden and peaceful end prevented the old friends from seeing him again in the familiar haunts at the Athenaeum and Burlington House.

Reference has already been made to Onslow's capacity for making a few intimate friends in his own subject with whom he continued to correspond to the end of his life. They saw much of each other, travelled abroad together, helped one another wherever possible, and in every way exercised powerful influence as a group. Hence the view, a false one, held by outsiders that he was distant and unapproachable. As he grew older the reverse was true—he enjoyed his clubs, a game of bridge, and conversation both with his peers and with younger men. His social gifts contributed greatly to the success of his Indian career. Those of us who battle to the end of life so as to continue to achieve in this harsh, invigorating climate should perhaps make allowances for the will to take things more easily under the Indian sun.

Scientific Work.

Forster was essentially an experimentalist and he had little interest in the theoretical aspects of chemistry. His only contribution to theory, a paper with F. P. Dunn (*J.*, 1909, **95**, 425) entitled " An interpretation of the Hantzsch–Werner hypothesis," was of minor importance. His first paper (with Meldola, *J.*, 1891, **59**, 59) dealt with a subject which was, at the time, of some importance, namely, the structure of the triazenes. Evidence was adduced that these were cyclic bodies and not hydrazones as had been suggested by Goldschmidt and his collaborators (*Ber.*, 1890, **23**, 505; 1891, **24**, 1000, 2300). His second paper, also with Meldola (*Proc.*, 1893, **9**, 7), recorded a convenient method for the preparation of a dinitro-α-naphthylamine. With Tilden he published three papers (*J.*, 1893, **63**, 1388; 1894, **65**, 324; 1895, **67**, 489) which dealt with the compound formed by the interaction of α-pinene with picric acid and with the addition of nitrosyl chloride to unsaturated compounds. It was to H. E. Armstrong, however, that Forster owed his introduction to the field of research to which he was to devote most of his active life. Armstrong was at the time greatly interested in the chemistry of camphor, and he suggested to Forster that he should investigate the action of nitric acid on αα′-dibromocamphor (I). Contrary to expectation the product was found to contain no nitrogen but was a lactone, dibromocampholid (II). Although, since the constitution to be assigned to camphor was still debatable, Forster could not assign a definite structure to dibromocampholid and the various substances which he prepared therefrom, this paper provides early evidence of Forster's experimental skill. Lapworth and his collaborators (*J.*, 1899, **75**, 992, 1134; 1900, **77**, 311; 1902, **81**, 17), also working under Armstrong's inspiration, were able to complete the work so ably commenced by Forster.

(I.) 

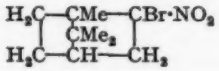
 (II.)

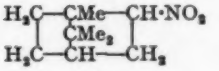
Forster next directed his attention to camphoroxime (*J.*, 1897, **71**, 191, 1030; 1899, **75**, 1141), a substance which was to provide him with problems to occupy his attention for many years. His earlier work, concerned with attempts to prepare the α-bromo-derivative, was unsuccessful, but he made two observations of some interest. Treatment of the oxime with methyl iodide gave methyl camphorimine in place of the expected methyl ether, whilst by the action of potassium hypobromite a substance of the formula $C_{10}H_{16}O_2NBr$ was obtained to which further reference is made below.

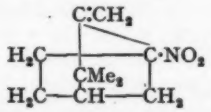
By reduction of the oxime with sodium in amyl alcoholic solution a convenient route to bornylamine was provided (*J.*, 1898, **73**, 386; with Hart-Smith, *ibid.*, 1900, **77**, 1152). He was thus able to show that the base previously prepared by Leuckart and Bach (*Ber.*, 1887, **20**, 104) by the action of amyl formate on camphor, followed by hydrolysis of the formyl derivative, was a mixture of the two isomeric bases, bornylamine and *neo*-bornylamine. Both these were fully characterised and in two subsequent papers (*J.*, 1899, **75**, 934, 1149) he drew attention to the effect of substitution and unsaturation on the optical rotatory power of these bases.

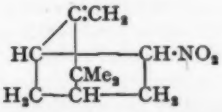
The marked effect of unsaturation on the rotatory power of camphor derivatives continued to interest Forster and in later papers (with Thornley, *J.*, 1909, **95**, 942; with Spinner, *ibid.*, 1919, **115**, 889) he discussed the remarkably high rotatory power of bisiminocamphor derivatives and in *p*-phenylenebisiminocamphor he recorded the highest rotatory power, $[\alpha]_D$ + 1509°, for any substance known at the time.

In 1900 (*J.*, **77**, 251) the first paper entitled " Studies in the Camphane Series " appeared, Part XLI published in 1926 forming the subject of his last scientific memoir. It was mentioned above that by the action of potassium hypobromite on camphoroxime a substance of the formula $C_{10}H_{16}O_2NBr$ was formed. This was now shown to be bromonitrocamphane (III) and from this by the action of alcoholic potassium hydroxide two isomeric 1-nitrocamphanes (IV) were prepared, whilst the removal of hydrogen bromide from (III) gave a nitrocamphene which may be represented by (V) or (VI).

(III.) 

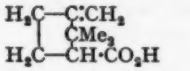
 (IV.)

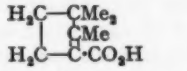
(V.) 

 (VI.)

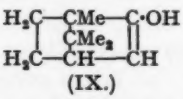
Unfortunately Forster did not determine whether his nitrocamphene was a *s*- or *t*-nitro-compound and since he was at the time unaware that the reaction involved a Meerwein–Wagner rearrangement he naturally concluded that it was a derivative of camphane. The reactions of bromonitrocamphane (III) and of nitrocamphene (V or VI) formed the subject of three further communications (*J.*, 1901, **79**, 544, 643; with W. A. Roberts, *ibid.*, p. 1003) in which the anhydrides of bromonitrocamphane, hydroxycamphene, and aminocamphene were described. Hydroxycamphene was found to undergo a remarkable change on treatment with bromine being converted into β-bromocamphor (*J.*, 1902, **61**, 264), a substance prepared more readily from Reychler's camphorsulphonic acid (Armstrong and Lowry, *J.*, 1902, **81**, 1462).

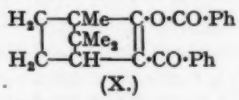
A further interesting observation was the conversion of bromonitrocamphane (III) into an unsaturated liquid acid, *infra*campholenic acid, by the action of aqueous sodium hydroxide. For this acid Forster (*J.*, 1901, **79**, 162) suggested the structure (VII) since it was isomerised by sulphuric acid to *iso*laurolonic acid (VIII). This formula for *infra*campholenic acid has since been shown to be correct.

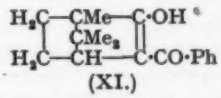
(VII.) 

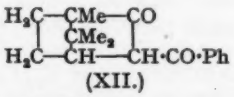
 (VIII.)

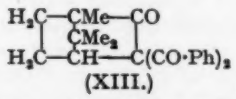
Forster was not unnaturally at first under the impression that his hydroxycamphene represented the enolic form of camphor (IX). He attempted therefore to prepare derivatives of this enolic form and in his first communication on this subject (*J.*, 1901, **79**, 987) he described the preparation of a dibenzoate by the action

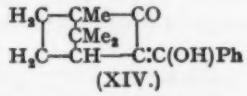

(IX.)


(X.)


(XI.)


(XII.)


(XIII.)

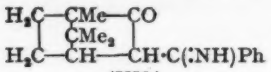

(XIV.)

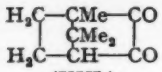
of benzoyl chloride on sodiocamphor. This he represented by (X) and the monobenzoate, obtained on hydrolysis, by (XI) which on digestion with formic acid passed into benzoylcamphor (XII). Later, however (*J.*, 1903, **83**, 98) he was able to show that the dibenzoate was actually (XIII) and the monobenzoate (XIV) since the latter gave on oxidation with chromic acid camphorquinone and on reduction benzylidene- and benzyl-camphor. The chlorination, bromination, and nitration of benzoylcamphor was also studied (with Micklethwait, *J.*, 1902, **81**, 167; with Jenkinson, *ibid.*, 1903, **83**, 537) when substitution occurred on the α-carbon atom. A further interesting observation was the formation of iminobenzoylcamphor (XV) by the action of ammonium formate on benzoylcamphor. This substance was prepared later (with Judd, *J.*, 1905, **87**, 372) by the action of phenylmagnesium bromide on α-cyanocamphor.

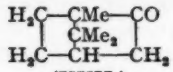
In 1903 (*J.*, **83**, 514) Forster commenced his study of the dioximes of camphorquinone and he isolated an unstable form of *iso*nitrosocamphor. This opened a field of research which was to be Forster's most outstanding contribution to the chemistry of camphor and incidentally formed the subject of his last scientific communication (with Rao, *J.*, 1926, 2670). Camphorquinone (XVI) can give rise to four monoximes represented by the abbreviated formulæ (XIX), (XX), (XXI), and (XXII). These are derived respectively from camphor (XVII) and *epi*camphor (XVIII).

*iso*Nitrosocamphor was first prepared by Claisen and Manasse (*Annalen*, 1893, **274**, 530) by the action of *iso*amyl nitrite on sodiocamphor. Forster was able to show that the stable form, m. p. 152°, was accompanied by an unstable form, m. p. 114°. The two derivatives are apparently present in approximately equal quantity but it remained for Forster and Rao to devise a convenient method for their separation. Forster (*J.*, 1905, **87**, 232)

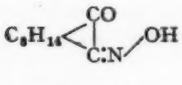
established the configuration of the two oximes assigning the *syn*-structure (XIX) to the stable form, m. p. 152°. This has since been shown by Meisenheimer and Theilacker (*Annalen*, 1930, **493**, 33) to be, in accordance

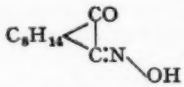

(XV.)

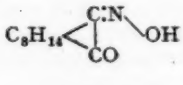

(XVI.)

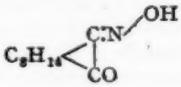

(XVII.)

(XVIII.)


(XIX.)


(XX.)

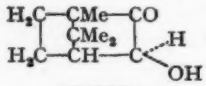

(XXI.)

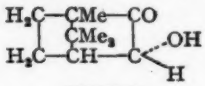

(XXII.)

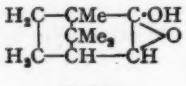
with modern theory, the *anti*-form (XX). Later the two *iso*nitroso*epi*camphors (XXI) and (XXII) were prepared simultaneously by Bredt and Perkin (*J.*, 1912, **101**, 1348) and by Forster and Spinner (*ibid.*, p. 1340). The configurations of these (stable form, m. p. 174°, and unstable form, m. p. 112°) were also determined; the former must now, however, be regarded as the *anti*- and not the *syn*-form as Forster postulated. Corresponding to the four monoximes of camphorquinone there are four dioximes which were all prepared by Forster and his collaborators, and in a remarkable memoir (*J.*, 1913, **103**, 3664) their configurations and their relationship to the monoximes were discussed. Whilst these configurations now require modification in the light of Meisenheimer's work the value of Forster's contribution remains undiminished and this must be regarded as Forster's greatest scientific paper.

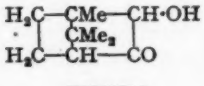
With various collaborators (with Zimmerli, *J.*, 1910, **97**, 2156; 1911, **99**, 478; with Kunz, *ibid.*, 1914, **105**, 718; with Saville, *ibid.*, 1920, **117**, 353) he extended his observations to the hydrazones, semicarbazones, hydrazo-oximes and oxime-hydrazones of camphorquinone and although they did not in all cases succeed in preparing all the possible isomerides they record reactions of very considerable interest.

In concluding our consideration of Forster's contributions to the chemistry of camphor reference must be made to one of his last papers (with Shukla, *J.*, 1925, **127**, 1855). By the reduction of camphorquinone with zinc dust in acetic acid solution Manasse in 1897 (*Ber.*, **30**, 689) had obtained two hydroxycamphors, which he regarded as the stereoisomerides (XXIII and XXIV). Whilst the first of these, α-hydroxycamphor, was undoubtedly a true hydroxycamphor (Lapworth and Chapman, *J.*, 1901, **79**, 382), Forster and Shukla, in agreement with Karrer and Takashima (*Helv. Chim. Acta*, 1925, **8**, 242), suggested that the β-form was actually the oxide (XXV). This suggestion was finally disproved by Bredt and Fischer (*J. pr. Chem.*, 1931, **131**, 49) who showed it to be a hydroxy*epi*camphor (XXVI).


(XXIII.)

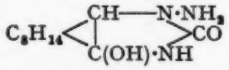

(XXIV.)

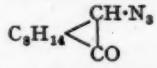

(XXV.)


(XXVI.)

Whilst retaining his interest in the chemistry of camphor Forster in 1908 broke completely new ground when he opened, in collaboration with Fierz, a series of communications entitled " The Triazo-group." This work, which in the short space of four years formed the subject of twenty-one memoirs, originated in the observation of Forster and Fierz (*J.*, 1905, **87**, 826) that camphoryl-ψ-semicarbazide (XXVII) (*ibid.*, p. 722) on

(XXVII.)




(XXVIII.)

treatment with nitrous acid gave camphorylazoimide (XXVIII). This substance was unique, since, although many triazo-compounds had been prepared previously, this was the first triazo-ketone to be described, whilst triazo-derivatives of acids, aldehydes, and alcohols were unknown. It was true that Curtius and Lang (*J. pr. Chem.*, 1888, **38**, 532) had recorded a triazoacetic acid but this had been shown later to be a bimolecular polymeride of diazoacetic acid.

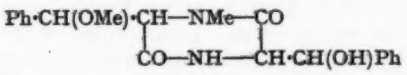
In their first communication (*J.*, 1908, **93**, 72) Forster and Fierz described the preparation of triazoacetic acid and triazoacetone, the method of preparation being to treat ethyl chloroacetate and chloroacetone respectively with sodium azide. This facile method of preparation was found to be of general application and a large number of mono- and bis-triazo-compounds were prepared and their reactions studied in great detail. Reference need only be made to three of these which Forster himself considered to be of peculiar interest, namely, the optically active modification of α-triazopropionic acid (with Fierz, *J.*, 1908, **93**, 1859) and the nitrosoazides of α-pinene and α-terpineol prepared by the action of sodium azide on the corresponding nitrosochlorides (with Newman, *J.*, 1911, **99**, 244).

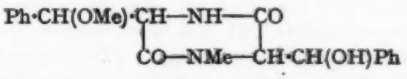
Whilst the explosive character of these compounds was recognised they appeared to have considerable stability. They could, when necessary, be purified by distillation under diminished pressure and analysed in the usual manner, and Philip (*J.*, 1908, **93**, 918) had determined the refraction and dispersion of many of them. However, in 1912 a disastrous explosion led to the cessation of work in this field. In collaboration with Withers (*J.*, 1912, **101**, 489) Forster had prepared αγ-bistriazopropylene, $N_3CH_2{\cdot}CH{:}CHN_3$, by the action of alkali on

αγ-bistriazo-β-chloropropane. The oil had been purified by distillation and its physical constants determined by Philip. On weighing out material required for the repetition of a nitrogen determination a violent explosion occurred and Dr. Withers was very seriously injured. In later years Forster used to tell with amusement of how he got rid of his specimens of triazo-compounds by dropping them from the windows of the Royal College of Science after his first attempt at destruction by dropping a kilogramme weight on to a specimen in a bucket of water had resulted in serious damage to the laboratory floor.

When Forster resumed work in the Davy–Faraday Laboratory at the Royal Institution in 1919 he came into possession of collection of chemical materials which, on the death of Mr. C. E. Groves, had been presented to the Royal Institution by the Misses Groves. Amongst these was a substance, picrorocellin, which had been obtained by Stenhouse and Groves (*Annalen*, 1877, **185**, 14) from the lichen, *Roccella fuciformis*, coming probably from the west coast of Africa. In collaboration with Saville (*J.*, 1922, **121**, 816) he was able to show in an elegant investigation that this substance, which had the composition $C_{20}H_{22}O_4N_2$, was the diketopiperazine derivative represented by either (XXIX) or (XXX). It was suggested that this compound was formed

(XXIX.)





(XXX.)

in the lichen by the intermolecular condensation of the two α-amino-acids, α-methylamino-β-methoxy-β-phenylpropionic acid and α-amino-β-hydroxy-β-phenylpropionic acid (phenylserine), or the corresponding acids in which the *N*-methyl group is transposed. In preliminary experiments, which had as their subject the synthesis of picrorocellin, Forster and Rao (*J.*, 1926, 1943) prepared the *cis*- and *trans*-modifications of phenylserine, but they were unsuccessful in attempts to convert these into a diketopiperazine derivative.

It is unfortunate that Forster with his remarkable powers of expression and exposition had so few opportunities of reaching a larger public, but he took full advantage of those which he had. As President of Section B at the Edinburgh meeting of the British Association in 1921 he delivered a brilliant address. Although this dealt with the recent advances of chemistry in the realm of the most complex of natural products, including chlorophyll and the anthocyanins, he succeeded in so presenting the facts that they cannot have failed to interest the audience and to have illustrated to the " common man " how important was the study of chemistry. His Benares address to the Indian Science Congress was in a more philosophic vein, the value of the study of science for all mankind. It shows Forster to have been not only a man of science but also a fine scholar.

E. F. Armstrong.
J. L. Simonsen.

BIRAJ MOHAN GUPTA.

1890—1945.

Dr. Biraj Mohan Gupta, Deputy Public Analyst to Government, United Provinces, died on May 26th, 1945, after a brief illness, at the Kharagpur residence of his eldest son, Capt. A. K. Gupta, Assistant Engineer, B.N. Railway.

Gupta was born in a village in Bengal on October 28th, 1890, and received his early education at Calcutta. After graduating from the Calcutta University, he migrated to Lucknow and studied in the Canning College from where he took the M.Sc. degree of the Allahabad University in 1914. Thereafter, he worked with Professor P. S. MacMahon on the " Composition of Milk at Lucknow," the results of which were published by the U.P. Government in the form of a printed booklet. Gupta worked as a teacher of Chemistry in the Lucknow Christian College for a while and on the introduction of the U.P. Prevention of Adulteration Act in 1915 he was appointed Assistant to the Public Analyst to Government, U.P. On the outbreak of the First World War, when Professor MacMahon went on active service, Biraj Mohan was appointed Assistant Professor of Chemistry in the Canning College, Lucknow, and also continued to be part-time Assistant Public Analyst to Government, United Provinces. In 1920 he proceeded to London to work under Professor Jocelyn F. Thorpe, and in the same year he was elected a Fellow of the Society, and became an Associate of the Institute of Chemistry. He obtained the Ph.D. degree of the London University, and published two papers in the *Journal*, on " An Investigation on the Influence of Negative Groups of Different Character on the Reactivity of Hydrogen Atoms Carried by the same Carbon Atom " and on " Formation of Bromine Derivatives of Carbon Compounds without the Production of Hydrogen Bromide ".

On his return to India in 1922, he was appointed a Reader in the Lucknow University, which post he continued to hold until 1929. During this period he also worked as part-time Assistant Public Analyst to Government, U.P.

On the reorganisation of the U.P. Government's Public Analyst Department in 1929, Dr. Gupta resigned his appointment in the University and became whole-time Deputy Public Analyst to Government, U.P., which office he continued to hold until the time of his death.

As a member of the Central Committee for Food Standards of the Government of India, Dr. Gupta has done valuable work in standardising foodstuffs in India. Among other publications, mention may be made of

" A note on the use of saccharine as a sweetening agent from the point of view of public health," printed in the Indian Medical Gazette, Vol. LXX, No. 9 (Sept., 1935).

Dr. Gupta, in collaboration with other assistants, worked on various problems connected with the analysis of foodstuffs, and read papers in the Indian Science Congress on many occasions.

An unassuming and quiet person, Dr. Gupta possessed a lovable temperament. He took keen interest in many spheres of activity, such as the Rotary movement. He was closely connected with the management of several educational institutions in Lucknow and was associated with many social organisations.

S. C. Roy.

ALFRED LUCAS.

1867—1945.

Alfred Lucas was born on 27th August, 1867, at Manchester. There is little available information concerning his early years, and Lucas rarely referred to them. He received his training at the Royal College of Science, and served as Assistant in the Government Laboratory for seven years. During this period he lectured for a short time at Birkbeck College. He became later a Fellow of the Royal Institute of Chemistry.

Having contracted tuberculosis, Lucas, on medical advice, went to Egypt in 1897. His health sufficiently recovered in the following year to allow him to become chemist to the Egyptian Salt and Soda Company under Mr. A. H. Hooker, known to Fellows of the Chemical Society as the donor, in 1930, of the mace. In 1899, Colonel (later Sir) Henry Lyons, Director of the Geological Survey Department, appointed Lucas chemist-in-charge of the small laboratory established by him chiefly for the analysis of Egyptian minerals. The work carried out in this laboratory rapidly increased in scope until all building materials and materials purchased by the Egyptian Government were analysed for compliance with the detailed specifications drawn up by Lucas. Later, the Egyptian Assay Office was attached to the laboratory and a Petroleum Section added to deal with oil investigations and royalties. Thus, Lucas established the present Egyptian Government Chemical Department of which he was Director until 1923. This Department was most efficiently staffed and, for the help given by it to the military authorities during 1914—1918, Lucas was awarded the O.B.E. He also received the Third Order of the Nile and the Fourth Order of the Osmania.

On his retirement, Lucas was able to take up the work in which he was most keenly interested, *viz.*, the application of chemistry in criminal and archæological investigation. He became chemist to the Antiquities Department and, as an essentially individualistic worker, he was much happier and even more successful than he had been as Director of a large Chemical Department. All his work was carried out with meticulous care and attention to detail, and his " Forensic Chemistry and Scientific Criminal Investigation " (a reprint of the fourth edition appeared after his death) affords evidence of Lucas's methods of solving problems and of his originality. This book will remain a standard on the subject for a considerable time.

Lucas created for himself a unique position in archæology, and especially in Egyptology. Almost from the time of his first arrival in Egypt, Lucas decided to make his home there, and Egyptology and archæological exploration in Egypt became his chief study. He wrote most interesting little books on " The Route of the Exodus " and on the history of Egypt and Libya and he was ready to make full use of the wonderful opportunity when his services were lent, in 1932, to (the late) Howard Carter for cleaning and preserving the huge wealth of objects found in the tomb of Tutankh-Amen (see " Chemistry of the Tomb ", " The Tomb of Tutankh-Amen ", vols. 2 and 3 by Howard Carter).

Probably Lucas's most important book was " Ancient Egyptian Materials and Industries ". In this fully documented and accurate work, Lucas did not hesitate to comment severely on mis-statements of previous writers. His " Antiques, Their Restoration and Preservation " incorporated his own practical experience as a chemist in this field. Lucas's unexpectedly long life was full of interest and this interest he willingly shared. His chief work was his own hobby and it was extremely well done. He was a chemist and a truly learned man, ever ready to place his amazingly detailed knowledge at the disposal of all who sought it.

He died, as he would have wished, in Luxor, on 10th December, 1945; he was about to attend a Commission on the Theban Tombs.

C. S. Gibson.

FREDERIC WILLIAM ROBINSON.

1889—1946.

Frederic William Robinson, elder son of the late Mr. and Mrs. Joseph Robinson of Grove House, Farnworth, near Widnes, recently died at Short Hills, New Jersey, U.S.A.

F. W. Robinson was born at Farnworth in 1889 and was educated at Widnes Secondary School and Liverpool University where he graduated with First Class Honours in the School of Chemistry and later obtained the M.Sc. degree in the same University. He won the Sir John Willox Research Scholarship and went to Germany to research in physical chemistry under Professor Haber at Karlsruhe. On the completion of this work he joined the firm of W. C. Heraeus at Hanau a. Main, where he developed the production of clear fused silica ware, and the manufacture of quartz mercury vapour lamps.

In 1912 he went to the United States at the foundation of Hanovia Chemical and Manufacturing Co., of Newark, New Jersey, an associated company of the Heraeus firm. He was made a director of this company in 1916, and in 1919 he joined the Board of the parent firm, and founded the Hanovia Quartz Lamp Company at Slough in this country.

Robinson was a well known member of the American Chemical Society, which has published some of his work, especially that in connection with air sterilisation for operating theatres and other places where sterile air is necessary. He took a great interest in the public affairs of Newark, New Jersey, and in its commercial development, having been President of the Chamber of Commerce of that city.

In 1917 Robinson married Marguerite Imfeld, an American girl of Swiss parentage, and her death in 1944 had a very depressing effect on his health. He is survived by three daughters.

D. G. BARKLA.

FREDERIC SWARTS.

1866—1940.

SWARTS, an honorary fellow of our Society, was rightly considered one of the leading Belgian scientists and had won a well-deserved reputation by his fundamental researches on organic fluorine compounds.

He was born in 1866 at Ghent at the time when his father was assistant at the university to Kekulé, whom he succeeded in the following year. At Ghent, Frederic Swarts received the degrees of Doctor in Natural Sciences in 1889, and Doctor in Medicine in 1899. He became assistant to his father, and from 1912 assumed the whole charge of teaching chemistry to beginners and advanced students at the university until his retirement in 1936.

His first paper was published in 1889 in the *Bulletin de l'Académie royale de Belgique*, where most of his work may be found; other papers were published in the *Bulletin de la Société chimique de Belgique* after 1912, and in the *Journal de Chimie physique* from 1919 onwards.

As far back as 1891, he could claim the synthesis of a new organic fluorine compound, trichlorofluoromethane; from then on, his discoveries in this line became more and more numerous. Such researches had long been hampered by the very great affinity displayed by fluorine for carbon and hydrogen and also by the difficulties and dangers inseparable from work with anhydrous hydrofluoric acid. Swarts was able to find a new method of approach by the use of other fluorinating agents.

Already, in 1892, he had shown that antimony trifluoride is particularly suitable, and in 1896 he began to use mercurous fluoride.

His first syntheses were made on a series of halogen derivatives of methane and ethane with different halogens in the same molecule, and the corresponding ethylenic derivatives; later, he synthesised racemic chlorobromofluoroacetic acid and monofluoroacetic acid. But by this method it was not possible to prepare compounds with three fluorine atoms on the same carbon; success here was achieved by the action of antimony trifluoride on phenylchloroform. From phenylfluoroform, ω-trifluoro-*o*-toluidine was prepared; this by careful oxidation gave trifluoroacetic acid, the strongest of all organic acids. Later Swarts succeeded in preparing trifluoroacetylacetic acid, the only keto-acid stable enough to be distilled without decomposition; he prepared also trifluoroacetone, trifluoroethyl alcohol, and hexafluoroethane. Finally, by diazotisation in concentrated hydrofluoric acid, he introduced fluorine into the aromatic ring itself.

Having at hand a great variety of organic fluorine compounds, Swarts pressed on with dogged perseverance in their study from the chemical as well as from the physico-chemical point of view. He showed for instance that the strength of the carbon–fluorine link explains the stability of fluorine compounds towards metals, bases, and water, and their inactivity to glass; it also explains the possibility of hydrogenating trifluorotoluene to trifluoromethyl*cyclo*hexane. The affinity of fluorine for hydrogen is apparent from the ease of the dissociation of secondary alkyl fluorides and the hydrogenation of compounds containing fluorine in the benzene ring, both with the loss of hydrofluoric acid.

In 1919 Swarts published an important contribution to the thermochemistry of more than sixty fluorine compounds. Besides adapting a very difficult technique, this research led to many interesting theoretical conclusions. The inner structure of the fluorine atom results in the narrowness of its external sphere of attraction and explains the remarkable volatility of its organic derivatives; difluoroacetic acid boils 45° lower than acetic acid, and trifluoromethyl cyanide 143° lower than methyl cyanide.

In 1923 came an important work on the refractometry of fluorine compounds; the molecular refraction of such derivatives was found to be lower than for the corresponding hydrocarbons; the atomic increment of fluorine was smaller than that of all other elements, even hydrogen. Finally, in 1931, he measured the viscosities of the same compounds.

During his forty years of research, Swarts had prepared many other halogen derivatives in a state of high purity and carefully determined their properties, so as to have the necessary materials for comparison with the corresponding fluorine compounds.

His ability as a teacher was of a high standard, as shown by the number of his pupils and the quality of his "Traité de Chimie minérale et organique."

Member of the Académie Royale de Belgique since 1904, holder of the decennial prize for chemistry and

physics in Belgium for the period 1909—1918, chairman of the Belgian National Committee for chemistry since its inception, of the Belgian Chemical Society, of the Solvay International Congress, corresponding member of the Institut de France, honorary member of the Royal Institution of Great Britain, etc., he was also the holder of many honorary degrees.

As a scientist, Swarts will be remembered as having during the last fifty years promoted to the highest degree the merits of the Belgian chemical school. He died in Ghent during the winter 1940—1941, from an infection of the lungs which, through the German occupation of Belgium, he had not been able to cure in a milder climate as he had formerly done each year.

Many facts made use of in this notice have been taken from the lecture that his friend, Professor Georges Chavanne of Brussels University, who also died during the war, presented in Ghent in 1936 at the meeting convened to do honour to Swarts on his retirement.

JEAN TIMMERMANS.

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